BRITISH MEDICAL JOURNAL

LONDON SATURDAY SEPTEMBER 29 1951

PRACTICAL ASPECTS OF RADIOACTIVE ISOTOPES IN RELATION TO MEDICAL TREATMENT*

BY

JOSEPH S. MITCHELL, C.B.E., M.B., Ph.D., D.M.R.

Professor of Radiotherapeutics, University of Cambridge

At the present time the use of artificial radioactive isotopes seems to be of considerable value in a few very limited fields of practical medical treatment. These applications are recent and still very incompletely understood, so that a conservative approach is essential.

Radio-phosphorus was first used clinically in 1936 by J. H. Lawrence and his colleagues at Berkeley, California. Its use was recommended in the treatment of chronic myeloid and chronic lymphatic leukaemia and polycythaemia vera by Lawrence, Scott, and Tuttle (1939) and Lawrence (1940). With accumulating experience, mainly during the last five years, it appears that the only disease in which radio-phosphorus therapy has given consistently better results than *x*-ray therapy is polycythaemia vera, and it is widely considered to be the treatment of choice in this not very common disease.

The use of radio-iodine in the treatment of thyrotoxicosis was described in 1942 by Hertz and Roberts, and by Hamilton and Lawrence. In the same year the first successful attempt to demonstrate selective concentration of radio-iodine in cancer of the thyroid was reported by Keston, Ball, Frantz, and Palmer (1942).

Many clinical trials of the use of radio-iodine in the treatment of thyrotoxicosis have been carried out, mainly in the U.S.A., and it is evident that selected cases respond very satisfactorily. In this country it has been thought wise to proceed rather cautiously, mainly because of concern over the possibility of the development of malignant changes, perhaps many years after the administration of the radio-iodine. While it is recognized that this risk is small and subsequently may be shown to be negligible, it is considered that at present more evidence is required, and that there is no justification for abandoning lines of treatment of proved value in favour of radio-iodine therapy. It is recommended as a general principle that in the treatment of thyrotoxicosis radio-iodine should not be given to patients of either sex under the age of 45 unless other methods of treatment have failed or are contraindicated. It is likely that with accumulating experience the use of radio-iodine will increase in the treatment of selected cases of thyrotoxicosis in which the thyroid gland shows a moderate degree of diffuse enlargement without clinically detectable nodularity or tracheal compression.

Radio-iodine is of value in only a small proportion of cases of carcinoma of the thyroid, probably in the region of 10%. Nevertheless, it is wise at the present time to test most cases of carcinoma of the thyroid for radio-iodine uptake, while emphasizing that surgery is the most important line of treatment and that *x*-ray therapy is still very useful.

A practical development which is becoming important is the use of artificial gamma-ray-emitting isotopes as substitutes for radium. Radio-cobalt appears to be satisfactory for interstitial and intracavity application and for use on external applicators and " moulds " ; its value has yet to be proved as a practical source in large teletherapy units. Meanwhile, radio-iridium seems to be of value in routine use as a gamma-ray source in a teletherapy unit.

Surface applicators utilizing the beta-rays of radio-phosphorus are entering the field of practical radiotherapy and appear to be useful in the treatment of selected cases of cavernous naevus in infants and children.

General Principles

The use of radioactive isotopes in treatment is essentially a form of radiotherapy, and in general requires the experience of a radiotherapist and the collaboration of a hospital physicist who is trained in radiotherapeutic dosimetry and also has gained experience of the techniques of handling and measuring radioactive isotopes. The clinical problems are among the most difficult in medicine, and include those met with in the uses of external radiation ; further, it is essential to try to estimate from the amount of the radioactive isotope administered the dose of radiation, specified in roentgen units or rep (roentgen equivalent physical), received by both the abnormal cells and the normal ones, especially the radio-sensitive cells of the bone marrow and reproductive organs and the less radio-sensitive cells of the kidney, which may be exposed during excretion. At the present stage, dosimetry is largely empirical, and correlation with the roentgen unit is an incompletely solved problem, though nevertheless the only available logical guide.

The risks of internal administration of any radioactive substance must be considered carefully for each isotope and especially for each patient, and may be far from negligible. Probably the most important unsolved question in radio-isotope therapy is whether there is any real risk of late carcinogenesis. One can be reasonably certain that with the present uses of radioactive isotopes

*Abridged version of a lecture delivered to the Society of Apothecaries of London on December 4, 1950.

the risk is small. Nevertheless, until it can be shown that the risk of carcinogenesis is negligible—for example, is in the region of 0.1% after 25 years—it is not in general justifiable to use radioactive isotopes in patients under 45 with non-malignant conditions, or in patients with cancer or allied diseases in whom the expectation of life exceeds five years. It is essential to assess quantitatively the risk of late carcinogenesis for comparison with the risks associated with other forms of treatment, including surgery.

The protection of staff and other patients is an important routine problem which can be solved by careful planning and organization, with constant supervision and forethought and frequent quantitative measurement and monitoring of the various radiation hazards.

The radioactive isotopes of interest in treatment are surveyed in Table I, in which an attempt is made to classify the value of the individual isotopes at the levels of practical treatment, clinical trials with definite promise of practical value, and preliminary studies. These isotopes fall into three main groups: those administered internally, those used as gamma-ray sources, and those used as external beta-ray sources. Each of these groups is considered, and the use of the more important individual isotopes is discussed in detail.

TABLE I.—*Therapeutic Applications of Radioactive Isotopes*

1. Administered internally:		
Selectively concentrated:		
Soluble inorganic ..	Practical treatment	P^{32}, I^{131}
	Clinical trials ..	I^{130}
	Preliminary studies	Ca^{45}, Sr^{89}, Ga^{72}, As^{76}, At^{211}, ThC
Colloidal inorganic	Clinical trials ..	Au^{198}
	Preliminary studies	$CrP^{32}O_4$, $Mn^{52}O_2$, Zn^{65}, Cu^{64}, Y^{90}, Zr^{95}, Ag^{111}
Organic	Experimental ..	
Uniformly distributed	Clinical trials ..	Na^{24}
2. Gamma-ray sources ..	Practical treatment	Co^{60}, Ir^{193}
	Clinical trials ..	Ta^{182}
		Na^{24} (Intracavitary application)
	Preliminary studies	Br^{82}, I^{131}
3. Beta-ray sources ..	Practical treatment	P^{32}
	Clinical trials ..	Sr^{90}-Y^{90}
	Preliminary studies	Ru^{106}-Rh^{106}, Ce^{144}-Pr^{144}

There are many tables of the properties of isotopes; one of the most useful is that published by Seaborg and Perlman (1948). Of especial medical interest is the catalogue (No. 2, published in 1950) of Radioactive Materials and Stable Isotopes of the Atomic Energy Research Establishment. The properties of selected isotopes of special interest in medicine have often been discussed (Lawrence and Hamilton, 1948; Clarke *et al.*, 1948; Mitchell, 1947a, 1947b, 1951); special mention must be made of a monograph by Mayneord (1950) and books by Low-Beer (1950) and Hahn (1951). From the point of view of protection and safe handling of radioactive isotopes, the "Introductory Manual on the Control of Health Hazards from Radioactive Materials," prepared for the Medical Research Council by the Ministry of Supply, Atomic Energy Research Establishment in 1949, is extremely useful.

Therapeutic Possibilities of Artificial Radioactive Isotopes Administered Internally

These are either more or less uniformly distributed throughout the body—as in the case of radio-sodium, Na^{24}, which has already received limited practical application to produce effects comparable to total body gamma radiation in the treatment of chronic myeloid and lymphatic leukaemia and polycythaemia vera (Hamilton and Stone, 1937; Thygesen, Videbaek, and Villaume, 1944; Lindgren, 1944; cf. Evans and Quimby, 1946; Evans, Lenz, Donlan, and LeMay, 1948)—or are capable of selective concentration in particular cells and tissues. Radio-phosphorus and the radio-iodines are practical examples of radioactive isotopes, used in soluble inorganic form, whose therapeutic action depends on selective concentration of the radioactivity in particular cells. The usual therapeutic applications of P^{32} in the form Na_2HPO_4 appear to be due to its synthesis into important cell constituents, including the ribo- and thymo-nucleic acids of multiplying cells, with greater rate of uptake into the dividing abnormal cells of malignant type than into the normal ones, which are probably also the less radio-sensitive. It is easy to understand the concentration of the radio-iodines by the thyroid in hyperthyroidism and not unreasonable to find that relatively few cases of carcinoma of the thyroid retain, even potentially, the function of iodine concentration. The radioactive iodine isotope I^{131}, of half-life 8 days, is the only radio-iodine now in practical use for treatment or tracer investigations; the pioneer clinical trials were made with mixtures of the 12.6-hour isotope I^{130} and smaller amounts of I^{131}, made by means of the cyclotron.

Therapeutic trials, mainly at the experimental level, have been carried out in the case of a number of other soluble inorganic isotopes which are to some extent selectively concentrated in particular cells or tissues. No promising results have been obtained by the attempted use in the treatment of osteogenic sarcoma of the weakly radioactive calcium isotope Ca^{45}, of half-life 152 days, and the radio-strontium Sr^{89}, of half-life 53 days (Pecher, 1941, 1942; Lawrence, 1942; Treadwell *et al.*, 1942), which is now recognized as at least potentially dangerous from the point of view of the risk of induction of malignant tumours of bone (Brues, Lisco, and Finkel, 1946; Lisco, Finkel and Brues, 1947). Recently, radio-gallium (Ga^{72}) has been shown to concentrate in areas of osteogenic activity (Dudley, Imirie, and Istock, 1950). The effect of the radio-arsenic, As^{76}, of half-life 26.8 hours, on the clinical course of patients with leukaemias, polycythaemia vera, multiple myeloma, mycosis fungoides, and metastatic carcinoma has been studied by Block, Jacobson, and Neal (1949), with the conclusion that under the conditions of this work As^{76} offers no advantages over types of therapy already in use. Of especial interest is the artificial alpha-ray-emitting element, astatine (At^{211}), of half-life 7.5 hours, which is selectively concentrated in the thyroid to almost the same degree as radio-iodine (Hamilton and Soley, 1940; Hamilton, 1942). Deucher and Leigh-Smith (1943) reported temporary retrogression of cutaneous metastases in a case of carcinoma of the bronchus by the use of thorium C, which is a bismuth isotope; I have used Th C in three extremely advanced cases and obtained indications of a high value of the order of 10 for the relative biological efficiency per ion pair with the alpha particles.

The possibility of selectively concentrated organic compounds containing radioactive isotopes, especially radio-iodine, is of great interest, but as yet this apparently promising but difficult line of approach has met with little success. It is relevant to mention the work of

Moore (1948) on the localization of cerebral tumours with radioactive di-iodo-fluorescein, and the studies by Seligman, Shear, Leiter, and Sweet (1948) with the polysaccharide from *Serratia marcescens* modified by the introduction of radio-iodine.

Numerous experimental studies of the therapeutic possibilities of insoluble radioactive colloids have been made. The main investigations have been of radioactive colloids which either are taken up more or less selectively by the reticulo-endothelial system after intravenous administration, or could be developed for local interstitial infiltration in and around regions of inoperable tumour, to effect what I suggest may be termed an "injection implant"; or could be introduced into the peritoneal or pleural cavity to inhibit the accumulation of effusions produced by secondary carcinomatous deposits. This method of approach appears likely to have considerable practical possibilities, especially in the use of radioactive colloidal gold for interstitial infiltration (Hahn *et al.*, 1947; Hahn and Carothers, 1950) and for intraperitoneal and intrapleural application (Müller, 1945, 1947a, 1947b, 1949). The other radioactive colloids used have included anhydrous chromic phosphate $CrP^{32}O_4$ (Jones *et al.*, 1944; Dobson *et al.*, 1948; Low-Beer, 1950); manganese dioxide, $Mn^{52}O_2$ (Hahn and Sheppard, 1946; Sheppard and Hahn, 1946a, 1946b); Zn^{63}, zinc sulphide in pectin solution (Müller, 1946; Müller and Rossier, 1947); colloidal radioactive copper, Cu^{64}—in the attempted treatment of malignant melanoma (Marcus and Rotblat, 1950); colloids derived from oxides and hydroxides of the fission products of yttrium, zirconium, and columbium (Dobson *et al.*, 1948; Gofman, 1949); and radio-silver, Ag^{111} (Hahn *et al.*, 1947). The localization of the various radioactive colloids after intravenous injection appears to depend mainly on the particle size.

Radio-phosphorus

Radio-phosphorus P^{32} has a half-life of 14.3 days and emits only beta-particles, of which the average energy is approximately 0.70 meV. Its relevant physical properties and approximate dosimetry are summarized in Table II. As with all isotopes, the term "dose" should, so far as is possible, be restricted to the dose of radiation in r or rep, and its use avoided when referring to the amount of isotope administered orally or parenterally.

TABLE II.—*Physical Properties and Dosimetry of Radio-phosphorus (P^{32})*

Half-life 14·3 days β-emitter. No gamma radiation.
Maximum energy of β-particles 1·712 ± 0·008 meV.
Mean " " " 0·70 meV.
Maximum range " " 0·82 cm. water.

1 μc. per g. of tissue delivers 38·5 rep per 24 hours (assuming constant concentration)

Without Excretion:
1 μc.* destroyed per g. gives a dose of 795 rep.
1 rep is delivered by 1·26 μc.δ per kg.

With Excretion:
Approximate calculations assume effective half-life 11 days. 1 μc. destroyed per g. gives a dose ~ 610 rep in mean time ~ 16 days. 10 rep is delivered by 1·15 millicuries* destroyed in a patient weighing 70 kg. (11 st.), assuming uniform distribution.

Differential Absorption Ratio (D.A.R.)
Approximate value for normal red bone marrow 1·5
and normal lymph node 2·5

Surface applicator: thin active layer.
Surface dose from 1 μc. per cm.^{2} is 5·1 rep per hour.

N.B.—These calculations are based on the relation that 1 r of the usual filtered gamma radiation from radium, of mean energy 0·8 meV, corresponds to the absorption of 93·1 ergs per g. of water, and 1 rep corresponds to the absorption of 93·1 ergs per g. of tissue.

* The curie is a unit of radioactivity defined as the quantity of any radioactive nuclide in which the number of disintegrations per second is $3{\cdot}700 \times 10^{10}$. One millicurie (mc.) is that quantity of any isotope which undergoes radioactive transformation at the rate of $3{\cdot}7 \times 10^7$ disintegrations per second; one microcurie (μc.) corresponds to $3{\cdot}7 \times 10^4$ disintegrations per second.

Radio-phosphorus is preferably administered intravenously in the form of an isotonic solution of Na_2HPO_4, which usually contains the order of 5 mc. of radio-phosphorus per ml.

However, oral administration is often convenient, and appears to be satisfactory if the phosphate solution is administered in the morning after a twelve-hour period of fasting and three hours before the next meal, with avoidance during the period before and during treatment of milk and foods rich in phosphorus, and medicines, such as iron compounds and alumina, which precipitate phosphate. Under these conditions it is safe to assume that 75% of the dose administered orally will be absorbed.

The results on excretion in Table II are based on the value of 11 days for the effective biological half-life of P^{32} in the human body. It is obvious that this value is not likely to be in general exact, especially in conditions of disease, and the biological half-life will vary in different individual patients and in different organs and tissues. However, this value enables one to make a crude approximation probably correct to within ± 50%, to correlate the dose of radio-phosphorus with the tissue dose in rep. The *mean life-time* of the isotope, which takes into account both radioactive and biological decay, appears to be the best analogue of the overall time of classical radiotherapy. The next approximation, which is often essential, is to measure the differential absorption ratio (D.A.R.)—that is, the ratio of the concentration of the radioactive isotope in a particular tissue to the mean concentration in the body as a whole. The possibility of delivering useful doses of radiation in any particular case may be determined by measuring the differential absorption ratio by means of tracer studies on biopsy and operation specimens (cf. Kenney, Marinelli, and Woodard, 1941), which, if possible, include normal tissues (Low-Beer, 1951, private communication). In this way, for example, it was found impossible to deliver therapeutically useful doses of beta-radiation from P^{32} to the primary tumour or lymph-node metastases in cases of carcinoma of the breast, and in osteogenic sarcoma.

Treatment of Polycythaemia Vera with Radio-phosphorus

The usual method of administration of radio-phosphorus, except in the treatment of polycythaemia vera, is based on the fractional dosage outlined by Low-Beer, Lawrence, and Stone (1942). In polycythaemia vera different patients vary greatly in their response to the same dose. It is very important to think in terms of the whole clinical picture as well as the haematological findings, and wise not to use radio-phosphorus in atypical cases, and essential to be certain of the diagnosis. The first injection of radio-phosphorus is usually of 5 to 7 mc.; Low-Beer (1951, private communication) recommends two initial injections each of 3 mc. on consecutive days. However, if oral administration is used a higher initial dose of 8 to 10 mc. is often required. Relatively smaller doses should be given to elderly patients. It is important to note that it usually takes three to six weeks before a significant fall in the red-cell count is observed, and two to three months after a single

dose of P^{32} for the red-cell count to settle down at a lower level because of the long life-span of the human red-blood cell.

In cases in which the polycythaemia is uncontrolled, venesection may be necessary to reduce the risk of thrombosis and haemorrhages during the latent period between the administration of the isotope and the production of a significant depression of erythropoiesis. The patient should have further blood counts every fortnight if possible. It is important to watch not only the red-cell count and the haematocrit reading but also the total and differential white-cell count, especially the absolute lymphocyte count, as in conventional radiotherapy, bearing in mind that the lower limit of the normal absolute lymphocyte count is approximately 1,200 per c.mm. and that it is not wise during radiotherapy to allow the absolute lymphocyte count to fall below 300 per c.mm. Platelet counts may be very useful in some cases. It is suggested that radio-phosphorus therapy should be used with great caution in patients with low platelet counts.

The second dose of radio-phosphorus should never be given in less than two, and preferably three, months after the first, and if there is no response and a second dose is necessary it should usually be smaller than the first, probably 3 to 5 mc. Once a satisfactory remission has been obtained the patient is seen for follow-up with full blood counts every two to four months. Recurrences of the polycythaemia are treated as in the initial course, but, one suspects, may ultimately need larger doses. Satisfactory remissions of 12 to 18 months appear to be common.

The advantages of radio-phosphorus therapy in polycythaemia vera are the reliable production of remission, the reduced incidence of thromboses and haemorrhages, the absence of immediate obvious toxic reactions, and the ease of administration of the treatment. Radio-phosphorus therapy certainly can produce good immediate palliative results and reduce the incidence of complications in some cases, but polycythaemia still remains an incurable disease. Its course is very chronic. The average duration of life appears to be about seven years. It is said that death usually takes place in three to eight years from diagnosis, but some cases live for 10 to 15 years and occasionally longer. There is some evidence for increased expectation of life after radio-phosphorus therapy (Lawrence, 1948).

The disadvantages of radio-phosphorus therapy in polycythaemia vera must be considered very seriously. It is impossible to reverse the effects of the radio-phosphorus or any other radioactive isotope after its internal administration, and one cannot detect beforehand the unusually radio-sensitive patient. Should an effective over-exposure occur, with the added risks of haemorrhage and infection, one would suggest the use of blood transfusions, penicillin, and "aureomycin." These measures may turn the scale in borderline cases, but there is no really effective antidote known.

It is important to recognize that all proliferating cells, normal and malignant, concentrate radio-phosphorus. The reality of the possible dangers has been demonstrated histologically by Platt (1947) in the organs of patients treated with radio-phosphorus. In many of these cases the doses of radio-phosphorus used were less than those generally used in the treatment of polycythaemia vera. In general, the histological changes were similar to those caused by external radiation. Striking changes were, of course, found in the bone marrow, lymph nodes, and spleen, although the latter organ was never reduced in size. Significant renal changes were observed and "can probably be attributed to the concentration that occurs in the nephron during the process of filtration and reabsorption." "Finally, serious consideration must be given to the changes in the testes and ovaries of patients who are in the reproductive period of life. Observation of these organs confirms the possibility that spermatogenesis and oogenesis may decrease or disappear, with development of sterility in young persons given radio-phosphorus."

One must attempt to assess the risk of genetic injury. Administration of 5.8 mc. of radio-phosphorus would deliver a dose of about 100 rep to the testis, assuming a value of 2, which is not likely to be too high, for the D.A.R. Genetic effects of repeated administration of radio-phosphorus are almost certainly additive. The most relevant experimental evidence is that in the mouse. New mutations occur in about 1% of sperm for each 100 r exposure at low-dosage rate; per 100 r there are 0.4% of chromosome translocations, 0.4% of recessive gene mutations, and about 0.3% of dominant gene mutations which would have immediate effects on the offspring (Charles, 1950). The problem of the genetic effects of radiation is very difficult (see Müller, 1950; Sewall Wright, 1950), and the quantitative application of these experimental results to man is very uncertain. However, from the point of view of the individual patient who is treated with radio-phosphorus in the reproductive period of life, it must be concluded that the risk of genetic injury is not negligible.

No final assessment can yet be given on the possibility or frequency of the induction of acute leukaemias, and perhaps also of osteogenic sarcoma, as a late complication of the radio-phosphorus therapy of polycythaemia vera. In a few cases an acute fulminating leukaemia has developed (Hall, 1948; Stroebel and Hall, 1951). It seems that this condition appeared very rarely in cases of polycythaemia vera treated before the use of radio-phosphorus (Tinney, Hall, and Giffin, 1943), despite the well-known natural history of polycythaemia vera and its tendency to the development of leukaemoid states with a terminal blood picture indistinguishable from that of chronic myeloid leukaemia in about 10% of cases. On the other hand, it is important to note that Lawrence (1948) after 12 years' experience of the radio-phosphorus therapy of polycythaemia vera had not observed any cases of acute fulminating leukaemia or any other evidence of carcinogenesis, so that the risk of this complication is almost certainly small.

From the evidence available it must be concluded that it is usually unwise to employ radio-phosphorus in the treatment of patients of either sex in the reproductive period of life, and caution is necessary in patients in whom the expectation of life exceeds five years.

It is important that radioactive isotopes should in no circumstances be used in the treatment of children suffering from non-malignant diseases. From a quantitative point of view, growth retardation may be expected after administration of about 0.8 mc. of radio-phosphorus in a child of 5 years weighing 40 lb. (18 kg.) if one can apply the results of experiments with growing rats (Kligerman, 1950). Further, there is no information about the really long-term effects of radio-phosphorus administered during the period of growth, and I personally would exclude the internal administration of this

isotope even in tracer doses to children under any conditions until more evidence is available.

It is useful to consider the effects and possible risks of larger amounts of radio-phosphorus than those usually given. Animal experiments show that in mice about 11% of delayed deaths were produced by 0.55 μc. per g. of body weight, and that the LD50 was in the region of 4 μc. per g. (Anthony and Snyder, 1947); for 42-day-old rats the LD50 was found to be about 3.6 μc. per g. If these values can be transferred to man, about 10% of delayed deaths would be produced by 35 mc. and the LD50 would be about 270 mc. Probably the largest safe amount for routine use is 10 mc.

Radio-phosphorus in Other Diseases

The results of radio-phosphorus therapy in diseases other than polycythaemia vera are much less satisfactory.

In *chronic myeloid and chronic lymphatic leukaemia* the results and limitations appear to be similar to those of *x*-ray therapy. The course of treatment often takes a longer time, and supplementary *x*-ray therapy to the spleen or to enlarged lymph nodes may be needed. It is certain that great care is necessary to avoid serious damage to the bone marrow. Even in the treatment of chronic myeloid leukaemia there appears to be a tendency to rely on *x*-ray therapy and to discard the use of radio-phosphorus as less safe. The risk of damage to the reproductive organs and of possible genetic injury are such serious matters that it seems to be an inescapable conclusion that radio-phosphorus therapy should not in general be used in patients in the reproductive period of life.

In most cases of *lymphosarcoma* treatment with radio-phosphorus is much less beneficial than with *x* rays. However, it is suggested that further clinical trials of radio-phosphorus, perhaps with supplementary *x*-ray therapy, are desirable.

The response of *Hodgkin's disease* to radio-phosphorus appears to be very variable and on the whole unsatisfactory, and inferior to that produced by *x*-radiation.

The limited results available do not encourage the use of radio-phosphorus in the treatment of *monocytic leukaemia* or *multiple myelomatosis*.

It is important to emphasize that radio-phosphorus, as used at present in the form of inorganic phosphate, seems to be of no therapeutic value in cancers generally. Clinical trials have been made in some cases of advanced cerebral tumours, and in some cases of anaplastic carcinoma and neuroblastoma where other methods of palliative treatment are contraindicated. However, in most cases of advanced malignant tumours, including those with multiple metastases, it is unjustifiable to give radio-phosphorus and usually much wiser and safer to employ the more accepted methods for palliative treatment and for the relief of pain.

Radio-iodine

The assumption of a uniform distribution of the radio-iodine is a simple one and appears to be of some value at the present stage, but it must be emphasized that it is incorrect in almost all cases of thyroid disease and in normal thyroid tissue, as has been shown by radio-autography.

The dose contribution received by the thyroid tissue from the gamma rays of radio-iodine is not important in treatment of hyperthyroidism, but is not negligible in the treatment of some cases of carcinoma of the thyroid. The accurate determination of the volume of thyroid tissue is an important unsolved question. Clinical examination, confirmed by studies of operation specimens and by making models, is difficult but is probably the best method at present. Radioactivity measurements on models in phantoms show that great errors are introduced by incomplete collimation of the counter, but are necessary to obtain information on back-scatter and extrathyroid radioactivity.

Oral administration of the radio-iodine is almost invariably used. However, it is much more satisfactory to use the intravenous route to administer the small tracer amounts—for example, 10 μc.—used in the investigation of cases of hyperthyroidism and other non-malignant diseases of the thyroid.

Treatment of Thyrotoxicosis with Radio-iodine

Radio-iodine therapy appears to have a very useful place in the treatment of those patients in whom: (1) the symptoms have recurred or persisted after surgery, and/or (2) there is failure of response or the development of toxic symptoms and intolerance following the use of the antithyroid drugs; or (3) surgery is contraindicated as unduly hazardous because of some serious complication such as age, poor general condition, heart disease, or threatened mental breakdown; or (4) surgery is definitely refused.

Most of the patients are over 45. It is evident that in most of them the disease has already proved resistant to other forms of treatment. In passing, it is suggested that *x*-ray therapy still has a limited field of application in the treatment of a few mild cases of primary thyrotoxicosis in which there is failure of response or intolerance to antithyroid drugs. Patients with recurrent thyrotoxicosis in whom the thyroid remnant has not appreciably enlarged appear to be especially suitable for radio-iodine therapy because further surgery is usually unsatisfactory and only small amounts of thyroid tissue can be removed; also these patients seem to be particularly liable to recurrence of the hyperthyroidism after treatment with antithyroid drugs.

The best results are obtained in those cases of thyrotoxicosis in which the thyroid gland shows a moderate degree of diffuse enlargement without nodularity or tracheal compression. Any clinically detectable nodularity of the thyroid before radio-iodine therapy is an indication for surgery. Poor results are sometimes obtained with radio-iodine therapy in cases with auricular fibrillation.

Other contraindications to radio-iodine therapy include (1) primary thyrotoxicosis in children and adolescents; (2) pregnancy, at least after the 12th week, when the foetal thyroid tissue starts to differentiate and concentrate iodine; (3) non-toxic goitre; and (4) uncertain diagnosis of hyperthyroidism.

Until the risk of late carcinogenesis can be assessed quantitatively it is not possible to compare the probably very small hazard to life of radio-iodine therapy with the known very small hazards of surgery and antithyroid drugs.

Before radio-iodine therapy all cases must be investigated carefully as in-patients. The importance of the general medical examination and assessment of the clinical condition cannot be over-emphasized. Records

of weight are very useful. The most essential laboratory investigations required are determination of the B.M.R. and plasma cholesterol, and serum protein-bound iodine if possible. The preliminary tracer investigation of radio-iodine uptake is usually essential for assessment of the amount of radio-iodine required for treatment, and often appears to be at least as useful an index of the severity of the disease as the B.M.R. determination, which estimates the response of the body tissues to the circulating hormone. The literature on the investigation of thyroid function and disease with radio-iodine is very extensive; of particular interest is the recent survey by Pochin (1950). It is necessary to estimate the percentage radio-iodine uptake into the thyroid tissue. The tests usually employ direct counts over the thyroid and, less frequently, measurement of the amount of radio-iodine excreted in the urine in the first 48 hours, about 90% appearing in the first 24 hours.

The estimation of the weight of the thyroid gland is subject to very considerable error, of the order of ± 50% even with practice. The normal gland weighs 20 ± 5 g.; the minimum detectable diffuse enlargement corresponds to a gland weight of about 35 g.; it is rare for a diffusely enlarged thyroid to exceed 100 g. in weight.

For the initial administration of radio-iodine, the amount to be given is calculated in terms of microcuries per gramme of thyroid tissue. Different workers have used a wide range of values, mainly lying between 50 and 250 μc. per g. There is as yet insufficient evidence for a decision on the best values. It is tentatively suggested that the initial amount should correspond to 60–100 μc. of radio-iodine collected per g. of thyroid tissue, so that the mean dose of beta radiation delivered is approximately 6,000–10,000 rep in a mean time of about nine days. The exact dose must be evaluated for each individual patient, taking into account the volume of thyroid tissue and the biological decay.

The uptake of radio-iodine into the thyroid should be re-determined for the therapeutic amount. The values of the fractional uptake and the biological decay are usually substantially the same for the tracer and the therapeutic amounts.

Clinical improvement is observed sometimes after 10 days, and usually after four weeks, from the time of administration of the radio-iodine. A similar interval is generally required before there is a definite decrease in size of the thyroid gland. The maximum clinical improvement and retrogression of the enlarged thyroid are usually reached at about three months after the initial treatment.

Between 70 and 90% of the patients treated appear to be controlled by the initial single dose. In those cases showing little response a second treatment, with a smaller amount, is often effective; occasionally a third treatment may be necessary. A few cases show a relapse after apparently responding to the first treatment, and then a second treatment is indicated. Some cases show a temporary hypothyroidism. However, a small but not negligible proportion of the cases treated develop myxoedema. The frequency of this complication varies between 0 and 17% in different reported series of cases. With initial amounts of radio-iodine corresponding to the collection of about 80 μc. per g. of thyroid the incidence of myxoedema seems to be in the region of 5%. Occasional cases have been reported in which an acute exacerbation of thyrotoxic symptoms followed radio-iodine therapy.

Radiation sickness is minimal after radio-iodine therapy, although a few patients receiving the higher doses have had transient nausea and malaise, and occasionally there has been a slight increase in the size of the gland and a slight fever for a few days. Blood count changes are probably never observed; the possibility of renal damage during excretion of the radio-iodine appears to be negligible in hyperthyroidism treated with radio-iodine I^{131}. The possibility of ovarian damage is considered to be negligible, and will be discussed in connexion with the use of much larger doses in the treatment of carcinoma of the thyroid.

The ocular manifestations respond as a rule much more slowly to radio-iodine therapy than the general condition and the thyroid size; progressive exophthalmos may develop after radio-iodine therapy as after surgery.

Pre-iodination and the use of antithyroid drugs interfere of course with the uptake of radio-iodine, and their administration must be discontinued at least four weeks before starting treatment with radio-iodine. Tracer studies of radioactive iodine uptake are essential to ascertain that the case is ready for radio-iodine therapy.

It is evident from this discussion that the use of radio-iodine therapy in hyperthyroidism requires much further investigation.

Mention must be made of the related subject of the treatment of selected euthyroid patients with intractable angina pectoris and congestive heart failure by destruction of the thyroid gland by means of radio-iodine (Freedberg *et al.*, 1950).

Treatment of Thyroid Carcinoma by Radio-iodine

1. General Indications

Radio-iodine therapy of carcinoma of the thyroid is still in an early stage of development and probably should be limited to a relatively small proportion of carefully selected cases. *X*-ray therapy is still very useful. Surgery is the most important first line of treatment, and its place must be considered in every case. Even if radical surgery cannot be carried out, it is usually desirable to remove surgically as much normal and malignant thyroid tissue as possible, including any technically operable metastases.

As a minimum, a satisfactory biopsy specimen should always be obtained. The importance of biopsy cannot be overemphasized, because without a biopsy it is very difficult to select the correct type of treatment. If the general condition is poor, intensive palliative *x*-ray therapy should be started at once, and is often of great value, especially in producing relief of pressure symptoms and relief of pain in metastases in bone. Advanced cases should not be regarded as hopeless. When the condition of the patient justifies it, as much of the tumour should be removed as possible and then *x*-ray treatment started. By this means real palliation is often possible, and useful life is sometimes surprisingly prolonged.

2. Examination of Cases for Radio-iodine Therapy

In addition to the histology it is essential to measure the uptake of radio-iodine, if any, in the primary growth and/or metastases with tracer amounts. The first step is external counting with a collimated Geiger or scintillation counter and mapping regions of uptake. However,

the best criterion for uptake is counting on a biopsy or surgical specimen after a tracer dose of 250 μc. of radio-iodine given three to four days before operation. Radio-autography of the specimens is a valuable supplementary research tool and requires tracer doses of the order of 1 mc. or therapeutic doses.

In addition to the general medical examination, the importance of which cannot be overemphasized, the most essential routine laboratory investigations required before and during treatment are the determination of the B.M.R. and plasma cholesterol and serum protein-bound iodine, and the full blood count, including total and differential leucocyte count and platelet count if possible.

3. Selection and Preparation of Cases for Radio-iodine Therapy

The not very common cases of anaplastic carcinoma of the thyroid, without demonstrable uptake of radio-iodine, will not benefit from radio-iodine therapy, but should be treated either by radical surgery with radical post-operative *x*-ray therapy or by radical *x*-ray or tele-radiation therapy only.

Probably all cases of the histologically differentiated types of thyroid carcinoma, including the papillary adenocarcinoma, which is relatively the most frequent type, should be considered for radio-iodine therapy if previous surgery is likely to have been incompletely curative, as is generally the case. The most favourable type is the so-called benign metastasizing struma. Normal thyroid tissue is usually the only strong competitor for radio-iodine. It now appears to be accepted that for these patients with proved residual or metastatic carcinoma of the thyroid the first step must be elimination of all the functioning normal thyroid tissue, either surgically or, in my opinion preferably, by means of radio-iodine.

Surgical removal of all normal thyroid tissue with as much tumour as possible has been widely recommended, despite its severity, largely because it is expeditious and because the remaining primary tumour and metastases can be tested for radio-iodine uptake, and the radio-iodine treatment started if indicated, without the delay of four to six weeks required in the case of radio-elimination of the normal thyroid tissue. However, after thyroidectomy a considerable proportion of the differentiated tumours which previously showed no uptake never develop a therapeutically useful uptake of radio-iodine in the residual tumour tissue or metastases. These cases should receive radical or palliative *x*-ray therapy without unnecessary delay. Accordingly, it is suggested that in most technically inoperable cases of histologically differentiated carcinoma of the thyroid, showing no evidence of radio-iodine uptake, it is wiser not to attempt surgical removal of the normal thyroid tissue but to rely on radiological thyroidectomy by means of radio-iodine. The minimum amount of radio-iodine required in most cases to destroy all the normal thyroid tissue is probably about 35 mc., administered orally on a single occasion. However, to secure a quicker and more certain effect, a larger amount such as 50 to 75 mc. of radio-iodine is often given, preferably in 25-mc. fractions on alternate days.

4. Technique of Radio-iodine Therapy and its Limitations

The principles of radio-iodine therapy in the selected cases of carcinoma of the thyroid are as yet incompletely understood. The most widely used technique is the method of multiple large "doses," which consists in the administration of a "therapeutic drink"—a term introduced by Paterson (1950)—of 100 mc. of radio-iodine (I^{131}) and its repetition at intervals of 8–12 weeks, until the uptake as estimated with tracer amounts falls to a very low level. If the patient is thyrotoxic the initial amount should be lower—for example, 25 mc. Apart from this limitation there is a recent tendency to use still larger initial amounts, such as 200 mc., which have apparently been safely repeated three or four times at intervals of four to six weeks. The largest single "dose" given appears to have been 315 mc. On the other hand, an alternative method, which I prefer, is the repeated administration of 25-mc. amounts at weekly intervals until the uptake of radio-iodine is abolished or greatly reduced. As yet there is insufficient experience to decide with certainty which is the best plan of treatment in any individual case. In those cases in which only one region of the primary tumour or one, or part of one, metastasis assumes the function of iodine uptake at any one time the repetition of treatment at intervals of three to six months would seem to be logical. A practical point which may be controversial is the suggestion that the patient can be sent home 48 hours after receiving 25 mc. of radio-iodine.

At the present stage it seems that the only possible plan is to state the estimated mean beta-ray dose in reps, assuming uniform distribution in a particular region of the tumour, and also if possible the approximate gamma-ray dose in reps and the corresponding mean lifetime of the radio-iodine in the region, taking into account both radioactive and biological decay. It is tentatively suggested that a mean beta-ray dose of at least 20,000 rep must be delivered with radio-iodine (I^{131}) in a mean time of the order of 10 days to each region of the more radio-responsive types of histologically differentiated thyroid carcinoma in order to produce prolonged retrogression. Some cases of carcinoma of the thyroid appear to be completely radio-resistant and radio-incurable, despite apparently adequate concentration of radio-iodine.

Radiation sickness is rarely a problem. The limiting factor in the safety of the large amounts of radio-iodine used is the dose of beta- and gamma-radiation received by the bone marrow and lymphoid tissue. This dose is probably between 1 and 2 rep per mc. As would be expected from this value, taking into account the mean lifetime of about 10 days, no changes in the peripheral blood count are usually found after 25-mc. amounts, but after the administration of 100 mc. most cases show temporary moderate leucopenia and lymphopenia. From the haematological point of view it would seem to be wise to avoid the repeated use of single amounts larger than 100 mc.

The radiation dose received by the ovaries is somewhat higher on account of the proximity of the bladder, probably about 3 rep per mc., of which about 2.3 rep is from gamma-radiation and 0.7 rep from beta-radiation. (There is no evidence of concentration of radio-iodine in the human ovary, but this factor must be considered, together with indirect effects *via* the pituitary.) It is therefore not unexpected that amenorrhoea with menopausal symptoms has been observed in some female patients after radio-iodine therapy of carcinoma of the thyroid (Trunnell *et al.*, 1949).

One of the major problems is that after removal or destruction of all the normal thyroid tissue at least

one-half and probably a considerably larger proportion of the cases do not develop any useful uptake of radio-iodine into the residual tumour or metastases. In some cases uptake has been observed to develop as late as six months after elimination of the normal thyroid tissue. It is evident that attempts must be made to increase the uptake by the tumour cells. These cases must be treated by radical or intensive palliative *x*-ray therapy without delay; it is conceivable that increased differentiation may follow the *x*-ray therapy and that this change may be associated with increased uptake of radio-iodine, but as yet there is no evidence of this effect. Of great interest are the attempts to induce uptake by injections of thyrotrophic hormone (Seidlin, Oshry, and Yalow, 1948) and by the use of thiouracil and its derivatives (Rawson *et al.*, 1949). Much further work is required in this field, especially with preparations of thyrotrophic hormone of known activity.

Radio-sodium Na^{24}

The results of the limited clinical trials suggest that radio-sodium is effective in the palliative treatment of some cases of chronic myeloid and chronic lymphatic leukaemia and polycythaemia vera, and in a few cases of other generalized radio-sensitive neoplastic diseases, but that, as yet, it has not shown sufficient advantage to justify its general use as a therapeutic agent in these conditions.

Radio-gold

For almost all the medical applications the isotope Au^{198} appears to be satisfactory, but in some instances higher specific activities may be desirable, and Hahn and Carothers (1950) have suggested the use of the carrier-free isotope Au^{199}.

It is suggested that there may be a restricted scope for the application of the "injection implant" in radiotherapy, especially in the treatment of inoperable recurrences of carcinoma of small volume which are inaccessible either to further surgery or to further irradiation by the usual methods. The limiting factor appears to be the capacity of the infiltrated tumour and adjacent normal tissue to retain the injected colloidal gold *in situ*. Secondary carcinoma in lymph nodes seems to be almost ideal in this respect, while carcinoma of the uterine cervix seems usually to be unsatisfactory. One must envisage the possibility of using injection implants of radioactive colloidal gold in conjunction with surgery in the treatment of some inoperable tumours. The development of the injection implant raises anew the questions of optimal dosage and tissue tolerance, especially in relation to the treatment of tumours which are regarded in the usual way as radio-resistant.

It seems likely that the intraperitoneal and intrapleural injection of radioactive colloidal gold may be accepted as a palliative method of treatment of some cases of peritoneal and pleural carcinomatosis to inhibit temporarily the accumulation of fluid.

Artificial Gamma-ray Sources in Radiotherapy

The possibility of production of artificial gamma-ray sources for use in radiotherapy became evident during the first few years of the working of the atomic pile. Probably similar ideas about this development arose simultaneously in several places. In a number of confidential reports and published papers (Dunworth and Mitchell, 1945; Mitchell, 1946a, 1946b, 1947a, 1947b) it was suggested that the most promising substitute for radium was radio-cobalt, Co^{60}, of half-life 5.3 years; the second choice was considered to be radio-tantalum, Ta^{182}, of half-life 117 days. Experimental studies of radio-cobalt were made by Mayneord (1946) and Mayneord and Cipriani (1947). W. G. Myers (1948) was the first to use radio-cobalt as a practical source for interstitial irradiation; he employed an alloy, "cobanic," consisting of 45% cobalt and 55% nickel, in the form of wire 1 mm. in diameter, cut to required lengths and activated in the pile. The soft beta-particles can be filtered off easily by thin-walled metal jackets—for example, 0.125 mm. of stainless steel. From a number of clinical trials it is becoming evident that radio-cobalt is a practical substitute for radium for employment in needles, tubes, and beads for interstitial implantation, for external use on "moulds" and other surface applicators, and for intracavitary application—for example, in the treatment of carcinoma of the uterine cervix and carcinoma of the bladder and antrum (Low-Beer, 1950). The possibility of production of large amounts of radio-cobalt of high specific activity in the pile raises the question of the practical development of large teletherapy units, which may compete with 2 meV *x*-ray therapy apparatus. The problems of protection and handling present substantial difficulties, but plans are being made for very large teletherapy units containing, for example, 1,000 curies of radio-cobalt (Grimmett, Fletcher, and Brucer, 1950).

Radio-iridium Teletherapy

Recently, the possibility of using other isotopes as gamma-ray sources in teletherapy units has been reconsidered. Radio-iridium Ir^{192}, of half-life 70 days, appears to be the most suitable of the shorter-lived isotopes for practical development. A radio-iridium teletherapy unit has been described by Freundlich, Haybittle, and Quick (1950). A unit containing about 20 curies of radio-iridium has been in routine use at the Radiotherapeutic Centre, Addenbrooke's Hospital, Cambridge, since May, 1950 (Figs. 1–4).

Details of the physical measurements made with the teletherapy unit are given by Freundlich, Haybittle, and Quick (1950).

The gamma-radiation of radio-iridium has a mean energy of approximately 400 keV; its half-value layer was found to be 8.1 mm. in copper and 2.4 mm. in lead. Hence the quality of the radio-iridium gamma-radiation is similar to that of filtered 800 kV *x*-radiation. From the point of view of application in radiotherapy this quality of radiation combines the advantages of the higher-energy gamma-radiation with considerably greater ease of protection.

The general appearance and constructional details of the radio-iridium teletherapy unit are shown in Figs. 1–4. The radioactive source itself is made up of four short concentric cylinders of 0.1 mm. thickness iridium metal mounted for mechanical strength on aluminium bases. The source (Fig. 4) is set into the side of the lead cylinder (2) of diameter 7.5 cm., which rotates inside the larger lead block of cylindrical section 12.5 cm. diameter and 17 cm. long with hemispherical ends. In the "off" position, the source is shielded by the thickness of the lead rotating cylinder (2). The head weighs about 60 lb. (27 kg.) and is mounted on a diagnostic *x*-ray stand. The source is rotated into the "on" and "off" positions by remote control. The half-life of Ir^{192} is 70 ± 3 days, so that it is necessary to have two sources, one for use in the unit and the other undergoing reactivation in

the pile. It has proved convenient to change the sources once a month. No serious practical difficulty is introduced by the decreasing dose rate; it is convenient to prescribe for each individual case a fixed time for each of the daily treatments in any one week, so as to give a constant weekly dose throughout the course of treatment.

The radio-iridium teletherapy unit in use gives a surface dose-rate of 12–13 r a minute at the usual focal-skin distance of 8 cm. The two standard applicators give circular fields of 3 and 5 cm. diameter. Smaller fields of other shapes can be obtained with the aid of apertures in lead diaphragms of 1 cm. thickness or occasionally

FIG. 1.—Radio-iridium teletherapy. General view of the Cambridge teletherapy unit in use in the treatment of a patient with intrinsic carcinoma of the larynx.

FIG. 2.—Radio-iridium teletherapy. Treatment of a patient with intrinsic carcinoma of the larynx, showing positioning with the aid of a perspex former.

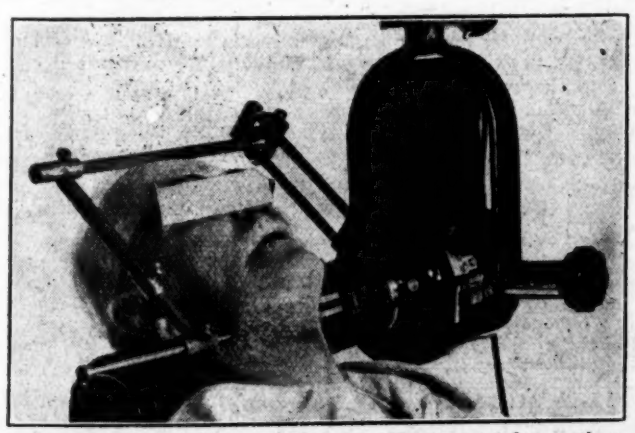


FIG. 3.—Radio-iridium teletherapy. Treatment of a patient with carcinoma of the posterior third of the tongue, showing positioning with the aid of a beam director.

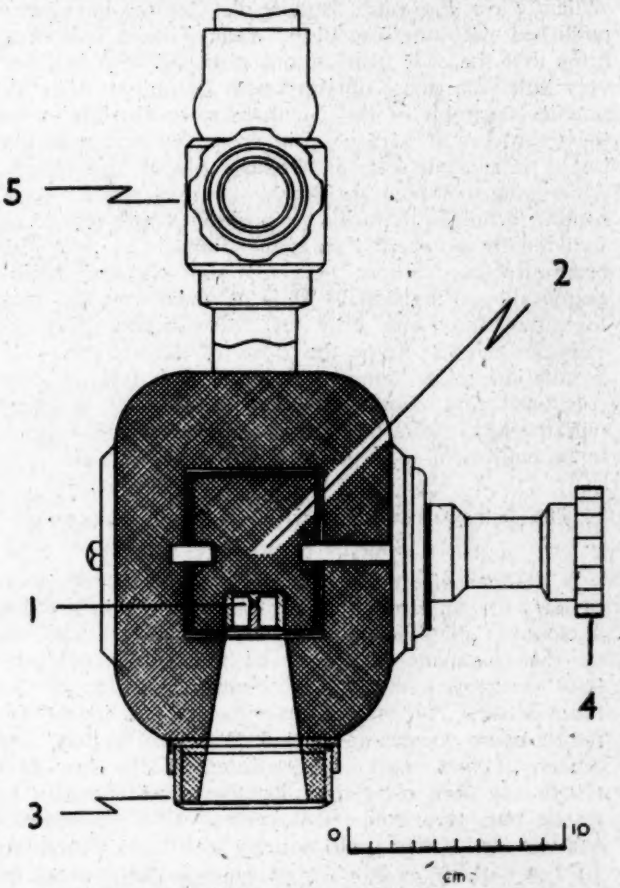


FIG. 4.—Radio-iridium teletherapy. Diagram showing the construction of the unit. (1) Source. (2) Lead cylinder. (3) External applicator. (4) Safety knob. (5) Knob for locking rotation round horizontal axis.

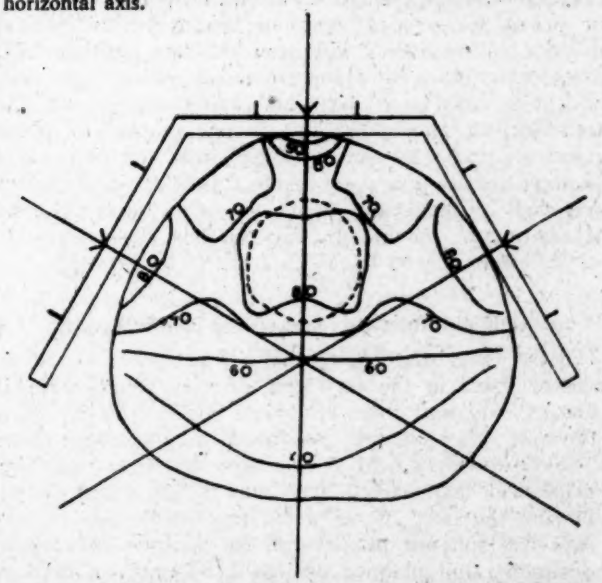


FIG. 5.—Radio-iridium teletherapy. Calculated dose distribution in the transverse plane through the lesion in a man of 54 with intrinsic carcinoma of the larynx (posterior two-thirds, right vocal cord. No glands). Histology: moderately differentiating keratinizing squamous carcinoma. Three fields: anterior, 3-cm. diameter circle; right and left lateral, 5-cm. diameter circles. The dotted line includes the region to be treated, which was determined with the aid of soft-tissue radiographs and tomographs. The correctness of the position of the former was checked radiographically.

more. Fields of diameter up to 7.5 cm. can be obtained by the use of longer F.S.D., but at present it is not practicable to exceed this field size on account of the inconveniently low dose-rate. Isodose distributions have been published. Routine use of the radio-iridium unit confirms that the dose distributions obtained with it differ very little from those obtained with teleradium units. A practical example of the calculated dose distribution in the treatment of a case of intrinsic carcinoma of the larynx is given in Fig. 5. Photographs of this patient undergoing treatment are shown in Figs. 1 and 2. As a routine technique the fields are positioned with the aid of individually prepared "perspex" formers or with the beam-directing calliper (Fig. 3) and checked radiographically. Provisionally it is assumed that the biologically equivalent dose of radio-iridium gamma-radiation is 1.2 times the dose of filtered 220 kV *x*-radiation under comparable conditions. It may be concluded that, from the point of view of practical radiotherapy, the radio-iridium teletherapy unit appears to be equivalent to a standard radium-beam unit.

Intracavitary Irradiation with Artificial Gamma-ray Sources in Solution

A number of studies have been made of the intracavitary use of gamma-ray-emitting isotopes in solution in closed elastic applicators. Most of this work has been on the treatment of lesions of the bladder. Müller (1949) employed solutions of cobalt chloride containing radio-cobalt, Co^{60} (together with sodium iodide for radiographic localization), and Wallace, Walton, and Sinclair (1949) used radio-sodium, Na^{24}. Low-Beer (1950) has been using a radioactive cobalt bead in an elastic bag as a convenient central source. Recently Walton (1950) has used bromide solutions containing Br^{82} of half-life 34 hours, which has the advantage over radio-sodium of beta-particles of much lower energy.

This type of treatment must be considered in those cases in which there are non-infiltrating carcinomatous or pre-malignant papillomatous lesions of the vesical mucosa arising over a wide area or from multiple foci. These cases have always presented a difficult problem, and it is considered that total cystectomy is not the treatment of choice for the greater number of these patients; partial cystectomy, diathermy, and deep *x*-ray therapy usually give poor results. It is obviously much too early to make any claims for intracavitary gamma irradiation of the bladder mucosa, but the results are of sufficient interest to justify further clinical trials.

Artificial Beta-ray Sources in Radiotherapy

It has long been known that the beta rays of radium are of value in the treatment of very superficial skin lesions, and that their biological effects are similar to those of other ionizing radiations in comparable doses. The view widely held at one time that beta rays were caustic in their effects was due to gross overdosage. During the past 20 years the therapeutic use of beta rays has suffered because of the absence of accurate dosimetry and planned dosage distribution in the case of the classical beta-ray plaque. However, recently, appreciable progress has been made towards solving these problems, and at the same time there has been a renewed interest in the therapeutic uses of beta rays from artificial radioactive isotopes.

Radio-phosphorus P^{32} has already been investigated as a practical external therapeutic agent in the treatment of skin lesions, including very superficial basal-cell carcinoma, hyperkeratosis, verruca of the hands, plantar and subungual warts, and cavernous haemangiomata (Low-Beer, 1946, 1947, 1950). In these pioneer clinical trials the applicators were cut out of a single layer of ordinary office-type blotting-paper, soaked in Na_2HPO_4 solution containing measured activities of P^{32}, and dried. It is safer and more convenient to enclose the dried radioactive blotting-paper applicator between two layers of "cellophane" film, which are sealed together around the edges.

The real need for accurate dosimetry with beta-ray applicators in r units or rep cannot be overemphasized. In the case of radio-phosphorus (see Table II) it is suggested that it is safer to rely on the dose rate measured with thin-walled ionization chambers than on the calculated values. The most valuable use of P^{32} beta-ray applicators so far appears to be in the treatment of selected cases of cavernous angioma in infants and young children. Measured surface doses of 500 r of beta-radiation, given in times of the order of one hour for the individual applications, seem to be satisfactory. The applicators are held in position with adhesive strapping and bandages. For larger naevi the area of the lesion can be subdivided into small rectangles and irregular areas with sides not exceeding 5 cm. and outlined with thin lead sheet; one area is treated each day, and the irradiation to each area is repeated if necessary at intervals of two to four months.

An applicator utilizing the beta-ray-emitting isotope Sr^{90} of half-life 25 years with its daughter product Y^{90} has been described by Friedell, Thomas, and Krohmer (1950), and has been employed in the treatment of superficial lesions of the eye.

Preliminary studies have been made with other beta-active isotopes (Freundlich, 1949). A group of isotopes has been studied in which there is a long-lived parent which emits low-energy beta particles, but has a short-lived daughter product which emits the required high-energy beta particles, together with weak gamma-radiation. The most promising isotopes of this group are the fission products, radio-ruthenium, Ru^{106}, and radio-cerium, Ce^{144}.

A further possible therapeutic application of beta-ray-emitting isotopes is their use as linear and point sources—"needles" and "seeds"—for *beta-ray implants*. Possible advantages of the beta-ray implant over the conventional gamma-ray implant are better dosage distribution, localization of the radiation field, and ease of protection.

I wish to thank my colleagues, especially Mr. H. F. Freundlich, Mr. R. S. Quick, and Mr. J. L. Haybittle, for their help in the work on which this paper is based.

BIBLIOGRAPHY

Anthony, D. S., and Snyder, R. H. (1947). MDDC, 881.
Block, M., Jacobson, L. O., and Neal, W. (1949). *J. Lab. clin. Med.*, **34**, 1366.
Brues, A. M., Lisco, H., and Finkel, M. (1946). MDDC, 145.
Charles, D. R. (1950). *Radiology*, **55**, 579.
Clarke, H. T., *et al.* (1948). *A Symposium on the Use of Isotopes in Biology and Medicine.* University of Wisconsin Press, Madison.
Deucher, W. G., and Leigh-Smith, A. (1943). *Schweiz. med. Wschr.*, **73**, 1092.
Dobson, E. L., *et al.* (1948). A.E.C.D.-2055 (U.C.R.L.-92).
Dudley, H. C., Imirie, G. W., and Istock, J. T. (1950). *Radiology*, **55**, 571.
Dunworth, J. V., and Mitchell, J. S. (1945). Reports to Montreal Laboratory of National Research Council, Canada, dated March 26, 1945, and October 17, 1945.

Evans, T. C., Lenz, M., Donlan, C. P., and LeMay, M. J. (1948). *Amer. J. Roentgenol.*, **59**, 469.
—— and Quimby, E. H. (1946). Ibid., **55**, 55.
Freedberg, A. S., Blumgart, H. L., Kurland, G. S., and Chamovitz, D. L. (1950). *J. clin. Endocrinol.*, **10**, 1270.
Freundlich, H. F. (1949). *Nature, Lond.*, **164**, 308.
—— Haybittle, J. L., and Quick, R. S. (1950). *Acta radiol., Stockh.*, **34**, 115.
Friedell, H. L., Thomas, C. I., and Krohmer, J. S. (1950). *Amer. J. Ophthal.*, **33**, 525.
Gofman, J. W. (1949). *J. Lab. clin. Med.*, **34**, 297.
Grimmett, L. G., Fletcher, G. H., and Brucer, M. (1950). 5th International Cancer Congress, Paris. *Abstracts*, p. 219.
Hahn, P. F. (1951). *A Manual of Artificial Radio-isotope Therapy*. Academic Press, New York.
—— and Carothers, E. L. (1950). *Nucleonics*, **6**, 54.
—— Goodell, J. P. B., Sheppard, C. W., Cannon, R. O., and Francis, H. C. (1947). *J. Lab. clin. Med.*, **32**, 1442.
—— and Sheppard, C. W. (1946). *Sth. med. J.*, **39**, 558.
—— —— (1948). *Ann. intern. Med.*, **28**, 598.
Hall, B. E. (1948). In *A Symposium on the Use of Isotopes in Biology and Medicine*, by H. T. Clarke *et al.*, p. 353. University of Wisconsin Press, Madison.
Hamilton, J. G. (1942). *Radiology*, **39**, 541.
—— and Lawrence, J. H. (1942). *J. clin. Invest.*, **21**, 624.
—— and Soley, M. H. (1940). *Amer. J. Physiol.*, **131**, 135.
—— and Stone, R. S. (1937). *Radiology*, **28**, 178.
Hertz, S., and Roberts, A. (1942). *J. clin. Invest.*, **21**, 624.
Jones, H. B., Wrobel, C. J., and Lyons, W. R. (1944). Ibid., **23**, 783.
Kenney, J. M., Marinelli, L. D., and Woodard, H. Q. (1941). *Radiology*, **37**, 683.
Keston, A. S., Ball, R. P., Frantz, V. K., and Palmer, W. W. (1942). *Science*, **95**, 362.
Kligerman, M. M. (1950). *Amer. J. Roentgenol.*, **63**, 380.
Lawrence, J. H. (1940). *Radiology*, **35**, 51.
—— (1942). *Proc. Inst. Med. Chicago*, **14**, 30.
—— (1948). *Brit. J. Radiol.*, **21**, 531.
—— and Hamilton, J. G. (1948). *Advances in Biological and Medical Physics*, vol. 1. Academic Press, New York.
—— Scott, K. G., and Tuttle, L. W. (1939). *New int. Clin.*, **3**, 33.
Lindgren, E. (1944). *Acta radiol., Stockh.*, **25**, 614.
Lisco, H., Finkel, M. P., and Brues, A. M. (1947). *Radiology*, **49**, 361.
Low-Beer, B. V. A. (1946). *Radiology*, **47**, 213.
—— (1947). *Amer. J. Roentgenol.*, **58**, 4.
—— (1950). *The Clinical Use of Radio-active Isotopes*. Thomas, Springfield.
—— Lawrence, J. H., and Stone, R. S. (1942). *Radiology*, **39**, 573.
Marcus, R., and Rotblat, J. (1950). *Brit. J. Radiol.*, **23**, 541.
Mayneord, W. V. (1946). Report to the Montreal Laboratory, National Research Council of Canada.
—— (1950). *Brit. J. Radiol.*, Suppl. 2.
—— and Cipriani, A. J. (1947). *Canad. J. Res.* (A), **25**, 303.
Mitchell, J. S. (1946a). *Schweiz. med. Wschr.*, **76**, 883.
—— (1946b). *Brit. J. Radiol.*, **19**, 481.
—— (1947a). *Brit. J. Cancer*, **1**, 1.
—— (1947b). *British Medical Journal*, **1**, 250.
—— (1951). In *Medical Treatment*, edited by G. Evans, p. 975. Butterworth, London.
Moore, G. E. (1948). *Science*, **107**, 569. See also Moore, G. E., Kohl, D. A., Marvin, J. F., Wang, J. C., and Caudill, C. M. (1950). *Radiology*, **55**, 344.
Müller, H. J. (1950). *J. cell. comp. Physiol.*, **35**, Suppl. 1, p. 9.
Müller, J. H. (1945). *Experientia, Basel*, **1**, 199.
—— (1946). Ibid., **2**, 9.
—— (1947a). *Radiol. clin., Basel*, **16**, 1, 82.
—— (1947b). *J. suisse Méd.*, **77**, 7, 236.
—— (1949). *Bull. schweiz. Akad. med. Wiss.*, **5**, 484.
—— and Rossier, P. H. (1947). *Experientia, Basel*, **3**, 75.
Myers, W. G. (1948). *Amer. J. Roentgenol.*, **60**, 816.
Paterson, J. R. (1950). *Brit. J. Radiol.*, **23**, 553.
Pecher, C. (1941). *Proc. Soc. exp. Biol., N.Y.*, **46**, 86.
—— (1942). *Univ. Calif. Publ. Pharmacol.*, **2**, 117.
Platt, W. R. (1947). *Arch. Path.*, **43**, 1.
Pochin, E. E. (1950). *Lancet*, **2**, 41, 84.
Rawson, R. W., Skanse, B. N., Marinelli, L. D., and Fluharty, R. G. (1949). *Cancer*, **2**, 279.
Seaborg, G. T., and Perlman, I. (1948). *Rev. mod. Phys.*, **20**, 585.
Seidlin, S. M., Oshry, E., and Yalow, A. A. (1948). *J. clin. Endocrinol.*, **8**, 423.
Seligman, A. M., Shear, M. J., Leiter, J., and Sweet, B. (1948). *J. nat. Cancer Inst.*, **9**, 17.
Sheppard, C. W., and Hahn, P. F. (1946a). *Sth. med. J.*, **39**, 562.
—— —— (1946b). *Fed. Proc.*, **5**, 227.
Stroebel, C. F., and Hall, B. E. (1951). In Hahn's *A Manual of Artificial Radio-isotope Therapy*, chapter 5.
Thygesen, J. E., Videbaek, A., and Villaume, I. (1944). *Acta Radiol., Stockh.*, **25**, 305.
Tinney, W. S., Hall, B. E., and Giffin, H. Z. (1943). *Proc. Mayo Clin.*, **18**, 227.
Treadwell, A. de G., Low-Beer, B. V. A., Friedell, H. L., and Lawrence, J. H. (1942). *Amer. J. med. Sci.*, **204**, 521.
Trunnell, J. B., Marinelli, L. D., Duffy, D. J., Hill, R., Peacock, W., and Rawson, R. W. (1949). *Trans. Amer. Goiter Ass.*, p. 330. Thomas, Springfield.
Wallace, D. M., Walton, R. J., and Sinclair, W. K. (1949). *Brit. J. Urol.*, **21**, 357.
Walton, R. J. (1950). *Brit. J. Radiol.*, **23**, 559.
Wright, Sewall (1950). *J. cell. comp. Physiol.*, **35**, Suppl. 1, p. 187.

THEORETICAL ASPECTS OF ISOTOPES IN RELATION TO MEDICINE*

BY

A. WORMALL, D.Sc.

Professor of Biochemistry in the University of London, at the Medical College of St. Bartholomew's Hospital

The use of radioactive and stable isotopes, the so-called "tagged" atoms or isotopic tracers, in the study of biochemistry and medicine is a development of recent times, and indeed this story is largely one covering the past 15 years. Now there is a veritable avalanche of papers describing the use of these tracers or labels in biochemical, physiological, and pharmacological research. Other papers describe their use in clinical medicine, where they serve as diagnostic aids (for example, the use of radio-sodium in the study of peripheral vascular diseases) and therapeutic agents (for example, radio-phosphorus in some of the leukaemias and radio-iodine in diseases of the thyroid).

It would be difficult to think of any major branch of biochemistry in which these tracers are not being used, usually with considerable success, and it may safely be prophesied that this technique will be applied to many branches of medicine and surgery. In my own department we are using both stable and radioactive isotopes to study immunochemistry and some problems of chemotherapy and cancer, and, where possible, this work is closely linked with investigations made by our clinical colleagues.

The varied nature of this relatively new application is well illustrated by reference to some of the ways in which isotopes have been used to label inorganic and organic compounds, and also organisms, both pathogenic and non-pathogenic. Penicillin, sulphapyridine, and vitamin B_1 have been labelled with radio-sulphur; amino-acids and antibodies with heavy nitrogen; and red cells, leucocytes, bacteria, viruses, trypanosomes, tsetse flies, and mosquitoes with radio-phosphorus and other radioactive isotopes. In other fields of investigation the isotopes have been used to "date" the Egyptian tombs and to calculate the age of the earth. For scientific detective work they offer a most attractive new tool.

It is obviously impossible to review the whole of this extensive field in one lecture, but I shall attempt to outline the more theoretical side of this new technique and say something about its historical development. A few typical examples of the use of isotopic tracers will be given.

Historical Development

This story would, of course, be incomplete without reference to the pioneer workers on nuclear physics. Lord Rutherford, who has been described as the founder

*Read to the Society of Apothecaries, London, on December 4, 1950.

of nuclear physics, Becquerel, with his fogged photographic plates, and Pierre and Marie Curie, with their isolation of radium, may be said to have led the way to this new Mecca. To Hevesy, however, must go the credit for first realizing the possibilities of the use of isotopes in biological investigation. In 1923 he used a radioactive isotope of lead (thorium B) in studies on plant metabolism, and it may be that even in those early days he was fully aware of the potentialities of the technique. At that time, however, his "labels" were limited to the few naturally radioactive isotopes which were available. Some 13 years later, after the discovery of artificially acquired radioactivity by the Joliot–Curies in 1933 and of deuterium (heavy hydrogen) by Urey in 1931, and the subsequent production of stable and radioactive isotopes in amounts sufficient for biological investigations, Hevesy was again a leader in the attack. His early dream of a fairyland where radioactive isotopes of most of the elements were available had come true. In the words of Dr. Rittenberg (1948), Hevesy might be regarded as "not only one of the fathers of the isotope technique but also the attending gynaecologist."

Pioneers in the application of deuterium and other stable isotopes were Schoenheimer and Rittenberg, and much of their early work, starting in 1935, and their fundamental results, are recorded by Schoenheimer (1942) in a book which should for ever rank as a classic in biochemistry.

Isotopes and Some of their Properties

Each chemical element is now known to exist in the form of two or more isotopes, the various isotopes of any one element having the same electrical charge on the atomic nucleus, but having different masses. Carbon, for example, can exist as isotopes of masses 10, 11, 12, 13, and 14—that is, as C^{10}, C^{11}, C^{12}, C^{13}, and C^{14}. Of these isotopes, C^{10}, C^{11}, and C^{14} are radioactive—that is, they are unstable and spontaneously undergo decomposition with the emission of particles or rays. The stable isotopes occur naturally, and carbon in organic compounds, CO_2, and carbonates consists mainly of C^{12} (98.9%) with 1.1% of C^{13}. Nitrogen, in the air and in amino-acids and proteins, is almost entirely N^{14} with a very small amount (0.38%) of N^{15}.

As the isotopes of any one element have the same number of positive charges on the nucleus, and therefore the same number of negatively charged electrons in the outer field of the atomic configuration, they have essentially the same chemical properties. Thus it can fairly safely be assumed that the "unnatural" isotope behaves like the normal one in metabolism in the animal body, though this is not strictly true in the case of the trio of hydrogen isotopes (H, deuterium, and tritium). A few typical isotopes which have proved of special use as tracers in biochemistry are listed in the Table.

*Some Isotopes Useful as Tracers in Biochemistry and Medicine**

Element	Stable		Radio (Half-life)
	Normal	Less Abundant	
Hydrogen	H^1	H^2 (0·016%) (deuterium)	H^3 (10·7–12·1 years) (tritium)
Carbon	C^{12}	C^{13} (1·1%)	C^{11} (20 min.) C^{14} (about 5,500 years)
Nitrogen	N^{14}	N^{15} (0·38%)	N^{13} (10 min.)
Oxygen	O^{16}	O^{18} (0·2%)	
Fluorine	F^{19}		F^{18} (112 min.)
Sodium	Na^{23}		Na^{22} (3 years) Na^{24} (14·8 hours)
Phosphorus	P^{31}		P^{32} (14·3 days)
Sulphur	S^{32}	S^{34} (4·2%)	S^{35} (87 days)
Calcium	Ca^{40}	Ca^{44} (2·1%)	Ca^{45} (180 days)
Iron	Fe^{56}	Fe^{54} (5·8%) Fe^{57} (2·2%)	Fe^{55} (4 years) Fe^{59} (47 days)
Zinc	Zn^{64} (49%)	Zn^{66} (28%) Zn^{68} (19%)	Zn^{65} (250 days)
Iodine	I^{127}		I^{130} (13 days) I^{131} (8 days)

* Data mainly from Seaborg and Perlman (1948).

The rate of decay of a radio-isotope can be accurately measured, and the half-life period, that period during which half the initial radioactivity is lost, is of considerable importance when we are choosing an isotope for tracer or therapeutic purposes. From the data given in Fig. 1 it will be seen that P^{32}, a radio-isotope of phosphorus, has properties which make it admirable for many biological studies; at the end of 28.6 days it will still retain one-quarter of the initial radioactivity, and, on the other hand, even if the whole of the P^{32} injected into the body were retained, the total body radioactivity due to P^{32} at the end of one year would be less than 1% of that originally injected. Isotopes of longer life, such as cobalt^{60}, zinc^{65}, and strontium^{90} (half-life of 25 years), should, of course, be used very cautiously in animal experiments, particularly where there is a possibility of the long retention of the isotope in some particular organ or tissue.

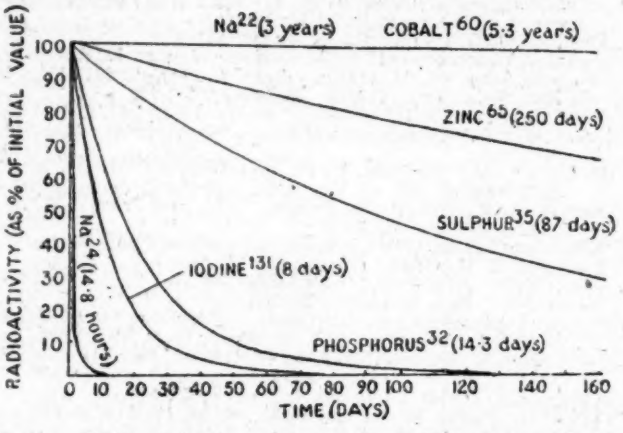


FIG. 1.—Radioactivity decay curves. The half-life period of the isotope is given in parentheses.

The value of the *stable* isotopes for medical research should not be underestimated, but for various reasons this paper is mainly concerned with the use of isotopes which are *radioactive*. Nearly 700 different radio-isotopes have now been characterized, and many are available in fair quantity for research and the treatment of disease. The choice of an isotope for investigation or therapy will naturally depend on various factors: the type of investigation or treatment planned, the half-life periods of the isotopes available, and the energy and the type of radiation which the isotope emits and the possibility of long retention of the isotope in the animal body.

Preparation of Radioactive Compounds

Radio-isotopes are prepared by exposing stable isotopes, in normal compounds, to the action of neutrons, protons, deuterons, or alpha particles, and the required isotope can often be made by two or more different methods. The commonly used P^{32}, for example, is made in the atomic pile at Harwell by neutron bombardment of either ordinary P (as red

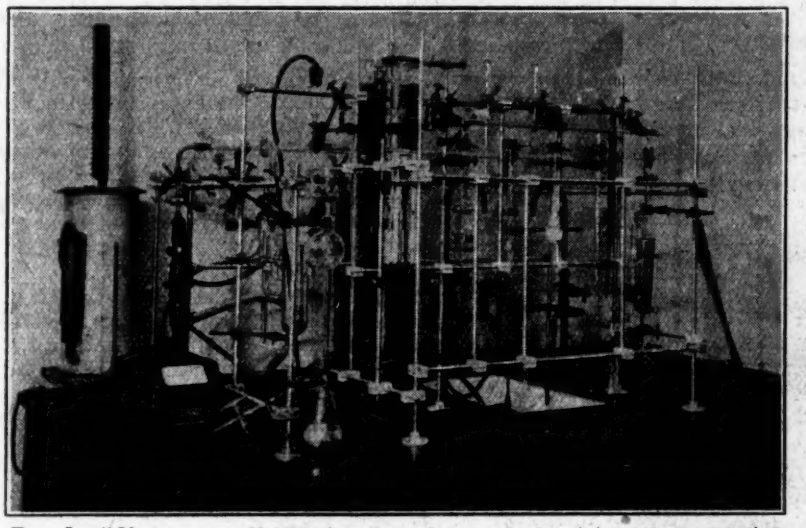


FIG. 2.—"Vacuum manifold" for the micro-synthesis of isotopically labelled compounds.

phosphorus) or ordinary S (as roll sulphur). The product obtained by the latter method contains little or no ordinary phosphorus and is therefore of high specific activity ("carrier-free"). The material supplied in either case will be inorganic phosphate containing P^{32}, and it is ready for use as such in experiment or therapy. Many of the radio-isotopes are produced most readily and most economically by the atomic pile, but the cyclotron still has its share of these duties.

For many investigations, clinical as well as laboratory, we want to introduce the radio-isotope into a drug, a protein, a fat, a red cell, a bacillus, or a yeast. Sometimes this is easy, but more often it requires considerable knowledge of what is almost a new chemical technique. In many cases special micro-methods have to be devised and the whole operation carried out in a special "vacuum manifold," to enable the synthesis to be effected with a very small amount of starting material. Fig. 2 is a photograph of an apparatus of this type which we are using extensively in my laboratory, and which was designed and erected by my colleague, Dr. V. C. E. Burnop.

In other cases biological methods of synthesis have proved extremely helpful. In effect, we employ animals, birds, bacteria, and yeasts as chemical assistants, and we induce them to use the administrated isotope to label some of the compounds they build up. In this way phosphoproteins, nucleoproteins, and phosphatides can be labelled with P^{32}, penicillin with S^{35}, and haemoglobin with radioactive isotopes of iron. My colleagues and I have during the past four years induced hens to "label" lipovitellin and phospholipin, so that we could use these marked compounds for our investigations on the chemistry of immunity. We inject P^{32} (as inorganic phosphate) into the hen, and the bird introduces the isotope into the egg-yolk proteins and phospholipins. We separate these labelled compounds from the egg-yolk and use them either for immunizing rabbits, to see where injected antigens go, or for precipitin tests, where radioactivity determinations allow us to estimate accurately the amount of antigen in a minute amount of precipitate.

Other workers have introduced radio-iron into red cells by giving the isotope to man or some other animal, and the cow and goat have been persuaded to introduce radio-phosphorus into the milk protein casein. These biological methods have several advantages over purely chemical methods for the isotopic labelling of proteins and other complex biochemical compounds, and the products obtained can be regarded as being completely physiological except for the presence of the label in some of the molecules.

The Detection and Estimation of Radioactive Isotopes

The radiations from a radioactive isotope are usually detected and measured by a Geiger–Müller counter system (Fig. 3), an ionization chamber, or a sensitive electroscope. In most tracer experiments the radioactivity of a weighed amount of the tissue studied is compared with that of the starting material used for the experiment. If required, the radioactivity of the tissue or an excreted compound can be expressed in terms of microcuries or millicuries (μc. or mc.); these are, respectively, one-millionth and one-thousandth part of a curie, and a curie corresponds to an amount of the isotope giving rise to 3.7×10^{10} disintegrations a second. Photographic methods can also be used, and this autoradiographic method is capable of showing in which minute structure the labelled element or molecule is deposited.

Measurements on the living animal can readily be made by using a Geiger-counter set, with the counter held near the surface of the body. For example, when the counter of one of our portable monitors is held near any part of a hen which has recently received an injection of P^{32}, the "click" of the loudspeaker and the movement of the needle on the scale indicate the radioactivity in that particular site of the body. The results show that injected phosphate rapidly diffuses throughout the body, though the site of injection shows much greater radioactivity than do other parts of the body for at least three to four days after the injection. When radio-iodine is injected the preferential accumulation of this element in the thyroid can readily be demonstrated on man.

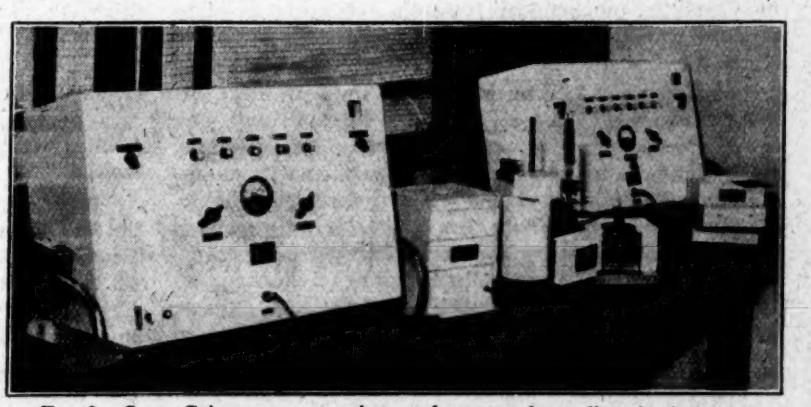


FIG. 3.—Some Geiger counter equipment for measuring radioactive isotopes.

Estimation of Stable Isotopes

Stable isotopes emit no characteristic radiations, and their estimation usually requires a mass spectrometer, a piece of equipment which is very complex and expensive (Fig. 4). Suitable mass spectrometers are, however, gradually becoming available in this country, and a more general use of stable isotopes as tracers should be of considerable value in the attack on many medical problems. For example, with the aid of a mass spectrometer my colleagues and I are studying the fate of injected nitrogen mustard, using as a label the stable nitrogen isotope N^{15}.

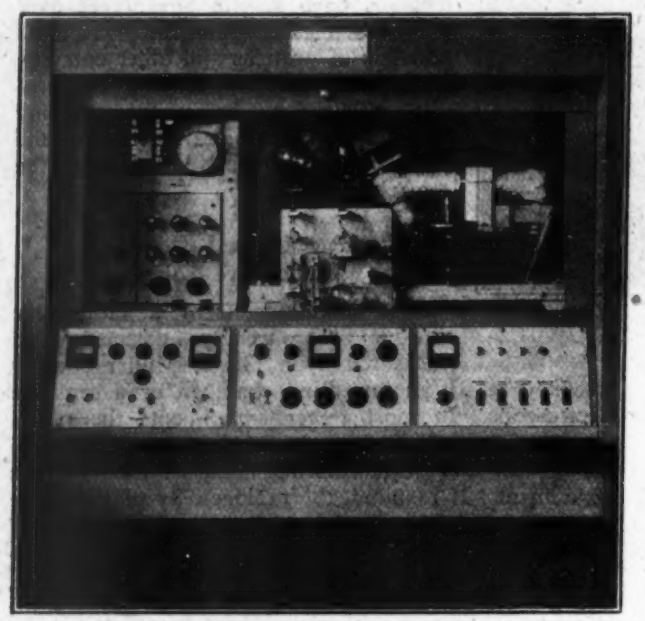


FIG. 4.—Consolidated-Nier isotope ratio mass spectrometer for the determination of stable isotopes.

Some Advantages of the Isotopic Tracer Technique

Throughout practically the whole history of biochemical investigation attempts have been made to find a method of labelling compounds in such a way that they could be traced in their passage through and excretion from the animal body. Benzene rings were used by Knoop, but methods of this sort had a limited application. The development of the general isotopic tracer method in the late 1930s truly opened up a new field in biochemical research, rendering possible types of investigation which are impossible by other techniques.

The isotopic tracer method, in its simplest form, involves the labelling of a chemical compound with one or more radioactive or stable isotopes. For example, the amino-acid methionine may be labelled with radiosulphur in one part of the molecule and, if double-labelling is wanted, with heavy (stable) nitrogen in another. The tagged methionine can then be administered to an animal and the tissues and excretions subsequently searched for the label or labels. A complete search should reveal the metabolic fate of the marked parts of the methionine molecule.

This isotopic tracer method has many advantages over other methods available for the study of metabolism, chemotherapy, and other branches of biochemistry and medicine—and here are some of them.

(1) The experiments can be carried out under physiological conditions, and in many cases on the living, intact animal. Carbohydrate metabolism can be studied, for example, without the administration of toxic phlorrhizin or alloxan, or the removal of the pancreas, to make the animal diabetic. Where radio-isotopes are used the rate at which the administered compound is distributed throughout the body and the rate of excretion of the label in urine, expired air, and faeces can be measured very simply.

(2) With a few exceptions, the labelled compound has, for all practical purposes, exactly the same chemical properties and the same metabolic fate as the normal unlabelled substance. Thus isotopic investigations on metabolism, etc., do not necessarily involve the use of compounds chemically foreign to the animal body. The only biochemically important exception to this general rule about the chemical identity of the isotopes of any one element is in the case of the hydrogen isotopes, and even here the quantitative differences involved do not normally invalidate biochemical investigations with these isotopes.

(3) Excessive dosing with the compound under investigation is not needed; indeed, where the compound is labelled with a radio-isotope the dose required may be only a small fraction of the amount normally administered.

(4) The actual radioactivity measurements can often be made on whole blood, separated blood cells or plasma, urine, or crude fractions of these materials. In other words, tedious time-consuming chemical separations are often unnecessary.

Some Disadvantages of the Isotopic Tracer Technique

This catalogue of advantages sounds almost too good to be true, and it would be unfair to omit the other side of the story. This technique has some disadvantages, and, although they are relatively few, they are very important. No investigator in this field of work can afford to disregard them.

(1) The radiations produced by the radio-isotope may have serious ill effects on the animal or tissue preparation studied, or on the investigator himself.

(2) The methods require the use of highly specialized apparatus and technique. Research of this type is best carried out as a team investigation, with the biochemist, physicist, and other appropriate experts all taking their full share of the responsibility.

(3) No suitable radio-isotope may be available for the planned investigation. The half-life periods of the radio-isotopes of the element being studied may, for example, be too short for normal-term experiments, or they may be so long that the treated animal may be subjected to "internal irradiation" for a dangerously long period.

(4) The isotopic tracer method merely involves following the label, and this fundamental point is often overlooked. The label should, of course, be fairly firmly attached to the tagged compound. If there is any doubt on this point—that is, if it is suspected that the tissues have simply "transferred" the label from one compound to the other—multiple tracers can be used; in other words, the compound can be labelled with two or more isotopes, in different parts of the molecule.

These few limitations should be kept in mind, but they do not seriously detract from the outstanding value of a new technique which has already helped to solve some of the most difficult problems of biochemistry and physiology. It should be emphasized, however, that investigations of this type, and their planning, are jobs for the expert, for the radio-isotopes can be very dangerous to the experimental animal and to the health and reputation of the investigator.

Health Hazards

Radioactive isotopes are dangerous tools, some much more lethal than others. Although there may be little risk where relatively small amounts of radio-isotopes are being used, it is important that the risks run by the investigator should always be recognized and reduced to a minimum. The laboratory, the apparatus used, and the individuals who handle the isotopes should be "monitored" frequently. I cannot very fully cover this subject of health hazards and the appropriate safety precautions; but I shall mention a few of the factors which have to be considered, as they cannot be disregarded even when only a few microcuries of radio-isotopes are being used.

So far as laboratory precautions are concerned it is often a good plan to adopt the meticulously careful technique of the chemist doing micro-analytical work plus that of the bacteriologist handling highly pathogenic organisms. The risk of ingestion or inhalation may be particularly serious, and among the factors which should be considered in this connexion are the following: the half-life of the isotope and the energy and type of radiation which it emits, the "biological life" of the isotope and the possibility of its selective deposition in bone and other tissues. As calcium and strontium become concentrated in certain portions of bone, radio-isotopes of these elements, particularly those of long life, are especially dangerous, and so is the long-life iron^{55}. Moderately dangerous isotopes include P^{32}, I^{131}, and Fe^{59}; Na^{24} and K^{42} are less dangerous.

These ingestion dangers must be considered in relation to the animals used in tracer experiments, as well as to the investigators. One of the chief features of the isotopic tracer method is the opportunity it provides for studies on the normal animal, and this object cannot be achieved if the animal receives a radio-isotope in amounts sufficient to alter its metabolism by internal irradiation. Furthermore, it should not be forgotten that malignancy can be induced by the administration of radio-strontium, radium, and probably certain other radio-isotopes.

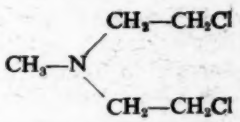
So far as the *stable* isotopes are concerned their use on man and other animals does not normally involve any hazard due to the nature of the isotope itself. Thus it seems probable that the use of these isotopes in clinical research will gradually become more popular.

Isotopic Tracers in the Study of Immunity, Chemotherapy, Etc.

The problems being studied by means of this new technique are legion, and it would need a whole series of lectures to cover this field adequately. However, perhaps I might be forgiven for selecting for this brief survey a few of the investigations which my colleagues and I have been carrying out. Towards the end of 1938 we started using radio-sulphur and deuterium to label mustard gas for a study of the action of this vesicant on animal tissues and for immunochemical studies. During the past twelve years we have developed a strong liking and respect for this tracer technique, and indeed we find that there are few biochemical investigations in which the tracer method cannot profitably be used.

For studies on immunochemistry, we have labelled antigens and antibodies with radio-isotopes (P^{32}, S^{35}, I^{131}), and with these tagged reagents we can readily determine the amount of each in the very small amount of precipitate obtained in the ordinary precipitin test. We hope, by these investigations, to learn more about antigen-antibody reactions and about the combining groups of these compounds (cf. Boursnell, Dewey, Francis, and Wormall, 1947; Banks, Francis, Mulligan, and Wormall, 1950). Using labelled antigens of this type, my colleagues and I, and investigators in other countries, are learning more about the distribution of injected antigens. We are also attempting to obtain specific deposition of radioactive compounds in selected parts of the body, including the reticulo-endothelial system and malignant tissues.

The nitrogen mustards have been used, and are still being used, in the treatment of Hodgkin's and certain related diseases, with results promising enough to justify further study of the effect of these compounds and related substances on the animal body. In our own investigations we are using one of the nitrogen mustards (methyl-*bis*(beta-chloroethyl) amine; code No. HN2), which we have synthesized in such a way that a fairly high proportion of its nitrogen is present as N^{15}, and we are also labelling the methyl group of the same compound with radio-carbon (C^{14}) as well. We hope that the use of these labels will enable us to find out how much of the injected nitrogen mustard goes into bone marrow, leucocytes, etc., and how much is decomposed or excreted in the urine.



Methyl-*bis*(beta-chloroethyl) amine
(Code No. HN2)

We are also using radio-isotopes in an attempt to determine the amount of the trypanocidal drug suramin which has to enter each *T. gambiense* trypanosome to kill or otherwise inactivate this organism. Such is the sensitivity of the methods of detecting radio-isotopes that we feel fairly confident that this goal should ultimately be reached. It is fairly certain that no other practicable method is available for such an investigation.

Some Examples of the Use of Isotopic Tracers in Metabolism

Because of the wealth of available material, it is almost embarrassing to have to select typical examples of isotopic tracer investigations which have made special contributions to our knowledge of metabolism. This tracer method is eminently suited to the study of biochemical reactions in the living cell.

One of the outstanding achievements of metabolic tracer work has been the tracking of the precursors of creatine, one of the important constituents of muscle. It has long been known that the animal body can synthesize this compound, and several theories have been put forward to explain the mechanism. Thanks to the isotope method and the skill and enthusiasm of those who used it in these investigations, the origin of each section of the creatine molecule can now be traced. In brief, it has been shown that arginine can supply the amidine group, methionine the methyl group, and glycine the rest of the molecule. As a scientific thriller, this story about creatine synthesis makes fascinating reading.

Another interesting story, and one which is only gradually being unfolded, concerns the synthesis of uric acid in the body. This fairly complex compound can be represented by the following structure, with the carbon and nitrogen atoms numbered for reference purposes.

In this case the investigators had to start with relatively few clues, and much of their early work involved the following of hunches. Fortunately, many of the guesses were inspired, and during the past three or four years much has been learned about the way in which uric acid can be built up in man and other animals. In this synthesis, as with those of creatine and the porphyrins, glycine occupies a key position, and it can serve as a source of the C—C—N structure occupying the positions 4, 5, and 7 in the uric-acid molecule. The rest of the picture is not yet complete, but it appears that CO_2 may supply the carbon atom in position 6, and that the carboxyl group of acetate (or some related compound) can furnish the other carbon atoms ; the nitrogen atoms in positions 1, 3, and 9 appear to come from the degradation of amino-acids in general. This information about purine synthesis in the animal body should materially advance our knowledge about the metabolism of the biologically important nucleic acids.

Concluding Remarks

The use of isotopic tracers has led to the discarding of the old theory of a dual type of metabolism in the cells of the animal body ; an *exogenous* metabolism of energy-bearing food material brought to the cell, and an entirely independent *endogenous* metabolism involving breakdown and repair of tissue cells. We now recognize that in the animal body there is a dynamic equilibrium, with food substances and cell components all forming what has been termed a "metabolic pool." All the tissues are supplied with this pool mixture of relatively simple compounds such as acetate, pyruvate, etc., and these compounds are used for combustion or tissue-building irrespective of their origin. This new concept, for which we are particularly indebted to Schoenheimer and Rittenberg, may be the isotopic tracer technique's finest achievement up to date.

We have used these new tools in my department for the past twelve years, and, as you will have gathered, I am not ashamed to admit my optimism about the future as regards the use of isotopes in medical research. Furthermore, we cannot exclude the possibility, though as yet it is no more than a possibility, that some investigator may one day find a satisfactory general method of using radio-isotopes to get specific irradiation of malignant tissues without damaging normal tissues. Fifty or even twenty-five years hence, the biochemist, the physicist, the clinician, and above all the patient may be able to assess in true perspective the relative gains and losses resulting from the developments which, incidentally or indirectly, produced the atomic bomb. When the balance sheet is drawn up it may well be that the gains will easily exceed the losses.

BIBLIOGRAPHY

The references marked with an asterisk are not specifically quoted in the text, but they are included here as they refer to textbooks and reviews which give good accounts of the use of isotopes in medical research.

Banks, T. E., Francis, G. E., Mulligan, W., and Wormall, A. (1950). *Nature, Lond.*, **165**, 111.

Boursnell, J. C., Dewey, H. M., Francis, G. E., and Wormall, A. (1947). Ibid., **160**, 339.

*Hamilton, J. G. (1942). *Radiology*, **39**, 541.

*Hevesy, G. (1948). *Radioactive Indicators*. Interscience Publishers, New York and London.

*Kamen, M. D. (1947). *Radioactive Tracers in Biology*. Academic Press, New York.

*Lawrence, J. H., and Hamilton, J. G. (1948). *Advances in Biological and Medical Physics*, vol. 1. Academic Press, New York.

*Mitchell, J. S. (1947). *Brit. J. Cancer*, **1**, 1.

Rittenberg, D. (1948). Cited from p. 150 of *Cold Spring Harbour Symposia, Quantitative Biology* ; vol. 13, *Biological Applications of Tracer Elements*. The Biological Laboratory, Cold Spring Harbour, New York.

Schoenheimer, R. (1942). *The Dynamic State of Body Constituents*. Harvard Univ. Press, Cambridge, Mass.

Seaborg, G. T., and Perlman, I. (1948). *Rev. mod. Phys.*, **20**, 585.

*University of Wisconsin Press (1948). *A Symposium on the Use of Isotopes in Biology and Medicine*. Madison.

SOME OBSERVATIONS ON ENDOGENOUS CORTISONE EXCRETION IN MAN

BY

C. L. COPE, D.M., F.R.C.P.

X. BOYSEN

AND

S. McCRAE, B.Sc.

(From the Postgraduate Medical School of London, W.12)

Recently (Cope, 1951) a preliminary account was published of a method capable of detecting the presence of cortisone-like activity in urine extracts from human subjects. The method depends on the measurement of the reduction in the number of circulating eosinophil cells in the blood of adrenalectomized mice after the injection of suitably prepared urine extracts. As cortisone and compound F are the only substances at present known which reduce the circulating eosinophil count of adrenalectomized animals, and as both these compounds have been demonstrated in extracts of human urine prepared in a similar manner to our own (Schneider, 1950 ; Zaffaroni, Burton, and Keutmann, 1950), it is assumed that the test is specific for the presence of these two substances.

The qualitative test can be made roughly quantitative by comparing the eosinophil drop produced by graded doses of cortisone acetate with that produced by the urine extracts. For this comparison to be valid it is essential that both be injected in the same type and volume of solvent, since the magnitude of the eosinophil drop produced by a given amount of cortisone acetate varies considerably with the conditions of the injection. This variation is presumably related to the differing rates of absorption of the compound from the injection site. Using such a quantitative test for small amounts of cortisone, it is possible to make observations on the

behaviour of endogenous cortisone under conditions of varying adrenal activity in man. The main interest of the urinary cortisone excretion lies in the presumption that changes in this excretion reflect similar changes in the blood concentration of the hormone. The amounts present in the circulating blood, with the exception of the adrenal vein, are too small to be detected with certainty, and recourse must therefore be made to such an indirect method for observing changes in adrenal activity. Some observations on the use of this biological method are presented in this paper.

For convenience the activity of urine extracts is referred to in terms of cortisone although compound F is probably also present. The relative proportions of these two compounds are, however, as yet unknown, and here the term "cortisone output" is used to denote the combined excretion of the two substances.

Methods

Suitable extracts of complete 24-hour collections of urine were made by the method previously described (Cope, 1951). Creatinine output was measured in all cases to provide some check on the completeness of collection of urine. In all cases hydrolysis was effected, before extraction with chloroform, by acidifying the urine to *p*H 1 with sulphuric acid and allowing it to stand at room temperature for 18 to 24 hours. Final extracts were stored dry in small glass-stoppered phials in the cold until required for assay. The period of such storage was usually about a week, but was occasionally longer. Immediately before injection into the adrenalectomized mice the extracts were dissolved in a small quantity of propylene glycol, which was then diluted with normal saline to a strength of 20%. The amount of propylene glycol used was such that the dose of extract to be injected into each mouse was contained in 0.5 ml. of the final 20% solution.

The sensitivity of the response varies considerably with the volume of the injection and also with the strain of mouse used. Under the conditions we have employed the optimum response is obtained with the equivalent of 50 to 80 μg. of cortisone per mouse, the eosinophil fall with this dose being between 50 and 80%. The size of the urinary aliquots for injection has therefore been so designed that an amount within this range might be expected in each dose. All injections have been made subcutaneously and no toxic symptoms have been noted.

Eosinophil counts were made on each mouse before injection and at four and six hours after. The phloxine-propylene glycol stain of Randolph (1944) was found the most convenient for revealing the eosinophils. No difficulty is encountered in taking sufficient blood from a tail vein if the room is kept warm enough. Maximum eosinophil cell depression may occur at four or six hours, and the lower of these two counts is used to calculate the percentage fall below the starting level.

Results

The Dose Response Curve

A typical dose response curve is shown in the continuous line in Fig. 1. In this figure the black dots represent the responses of individual mice to the injected cortisone acetate. Considerable variation in response occurs with the smaller doses, but this variability becomes less with doses of 50 μg. and over. The greatest constancy of result is found with doses of 50 to 80 μg. of cortisone per mouse.

Accuracy of assay will depend on the number of mice used for each comparison. In these preliminary studies, where greater accuracy was not sought, each unknown extract was injected into three mice and the mean percentage eosinophil drop in the three mice was calculated and used to read off the approximate cortisone equivalent from the calibration curve.

The response curve shown in Fig. 1 cannot be used without confirmation in other laboratories. The interrupted line to the left represents the response when

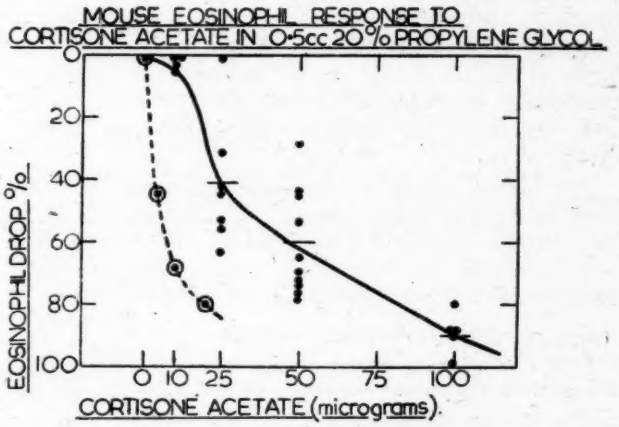


FIG. 1.—Dose response curve for cortisone acetate.

cortisone acetate is injected in a smaller volume in saline suspension into another strain of mice. Under these conditions the mice were nearly five times more sensitive. Nevertheless the white mice we have used were chosen in spite of their relative insensitivity because they were more readily available. Similarly, the constant but relatively large volume used for the injections allowed the uniform handling of urine extracts which varied in bulk and in physical properties.

Normal Cortisone Excretion

For the normal group we have selected patients whose adrenal conditions could be regarded as basal. Only those who had not been subjected to a recognizable acute or chronic stress during the preceding three weeks

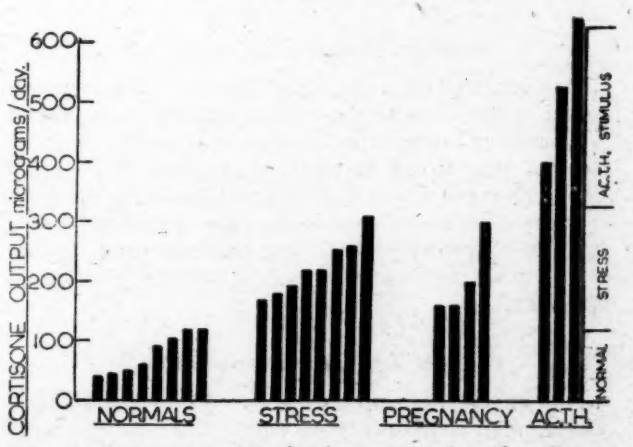


FIG. 2.—Urinary excretion of endogenous cortisone in quiescent normals, stress due to medical disease, late normal pregnancy, and after A.C.T.H. therapy.

were considered eligible, and those chosen consisted of patients in the last week of a routine course of bed rest and diet for duodenal ulcer and certain neurological cases admitted for investigation. Eight such cases, all males, have been studied, and these showed cortisone excretions ranging between 40 and 120 μg. a day (Fig. 2). These normal figures are similar to the normal range found by Venning, Kazmin, and Bell (1946) when using their glycogen-storage method.

Cortisone Excretion in Medical Stress

It is now generally recognized that the adrenal cortex is rapidly stimulated to increased activity by a wide variety of noxious stimuli. To indicate the great variety of such adrenal stimuli to be found in general medical disorders we have deliberately chosen a heterogeneous series of disease states. In all of these the output of cortisone in the urine was raised well above the resting level, and indeed no overlap occurred between the two groups (Fig. 2).

The actual output of cortisone estimated in these cases of medical stress ranged from 180 to 320 μg. a day. The following are brief details of the individual cases included in this stress series. The cortisone excreted each day is indicated in parentheses.

Case 1.—Status asthmaticus. Severe. (260 μg.)

Case 2.—Coronary infarct three weeks previously. Mild. No present symptoms, but still high E.S.R. (195 μg.)

Case 3.—Bronchopneumonia. Mild. Febrile. (220 μg.)

Case 4.—Obstructive jaundice; carcinoma head of pancreas. Serum bilirubin 18 mg. per 100 ml. (170 μg.)

Case 5.—Pneumococcal meningitis. Male aged 56. Three days before death. (220 μg.)

Case 6.—Bronchopneumonia. Moderate. (255 μg.)

Case 7.—Congestive cardiac failure with dyspnoea, mild cyanosis, and slight oedema. (180 μg.)

Case 8.—Diabetic ketosis. Drowsy but not comatose. (320 μg.)

Case 9.—Subacute peritonitis. (250 μg.)

In these cases the increase in cortisone output was not well related to the clinical estimate of the severity of the medical stress. It is of interest that the lowest cortisone excretion of the group was in the case of severe obstructive jaundice. This was surprising in view of Hench's discovery of the beneficial effects of jaundice on the course of rheumatoid arthritis.

Cortisone Excretion in Late Pregnancy

In the eighth month of normal pregnancy the cortisone output in the urine is also raised, and the range found in a series of seven cases of normal pregnancy was the same as that found in cases of medical stress—from 170 to 300 μg. a day (Fig. 2). This increase in excretion of adrenal cortical hormones has previously been reported by Venning (1945), who obtained values similar to our own although she used a different method of bio-assay.

Effects of A.C.T.H. on Cortisone Output

An increase in output of cortisone considerably greater than that usually encountered in medical stress can be produced by five or six days' treatment with

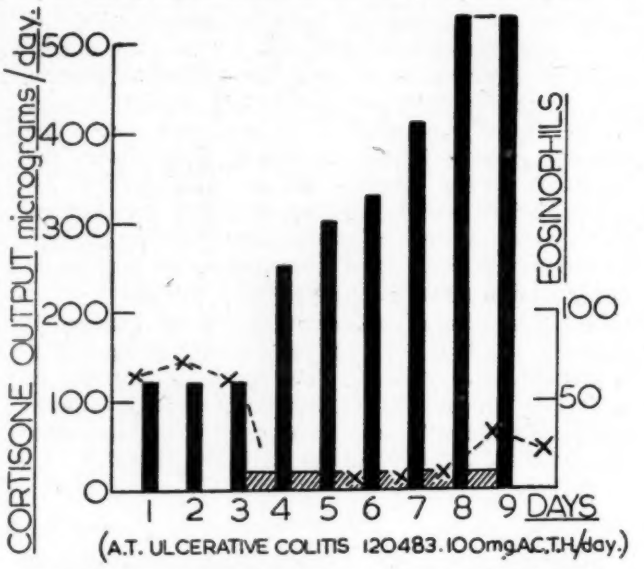


FIG. 3.—Effect of A.C.T.H., 100 mg. daily from the third to the ninth day on cortisone output (black columns) and eosinophil count (crosses) in a patient (A.T.) with ulcerative colitis.

A.C.T.H. The right-hand columns in Fig. 2 indicate the levels achieved after six days' A.C.T.H. therapy in three typical examples. That the rise is progressive over several days is shown by Case A.T. (Fig. 3), a male suffering from mild ulcerative colitis who received 100 mg. of A.C.T.H. daily for six days. Individual variations in adrenal response to A.C.T.H. have, however, been suspected on clinical grounds, and they do indeed seem to occur. Thus Case P. (Fig. 4), who was suffering from scleroderma, was given the same dose of A.C.T.H. for six days; but the response was relatively poor, the cortisone output not rising above 250 μg. daily. In this patient A.C.T.H. therapy was originally delayed because of a mild attack of pneumonia, which responded to antibiotics. At the height of this infection cortisone excretion was raised above normal resting levels by the stress, and the fall to normal output during convalescence is well shown in Fig. 4. In this case the administration of A.C.T.H. for six days produced a scarcely greater cortisone output than had the stress of the pneumonia. This relative insensitivity

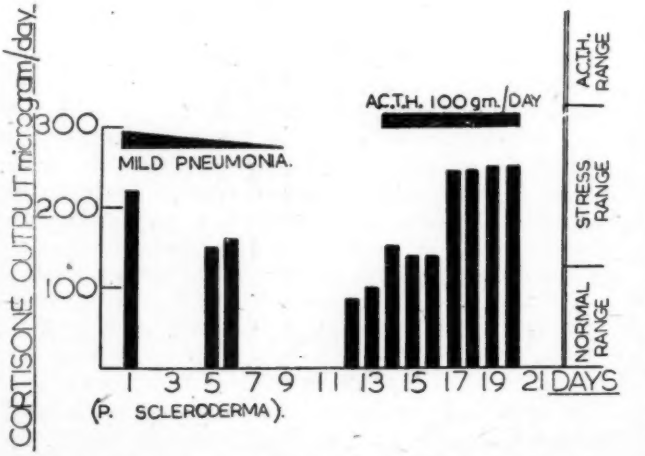


FIG. 4.—Relatively poor response to A.C.T.H. in a case of scleroderma.

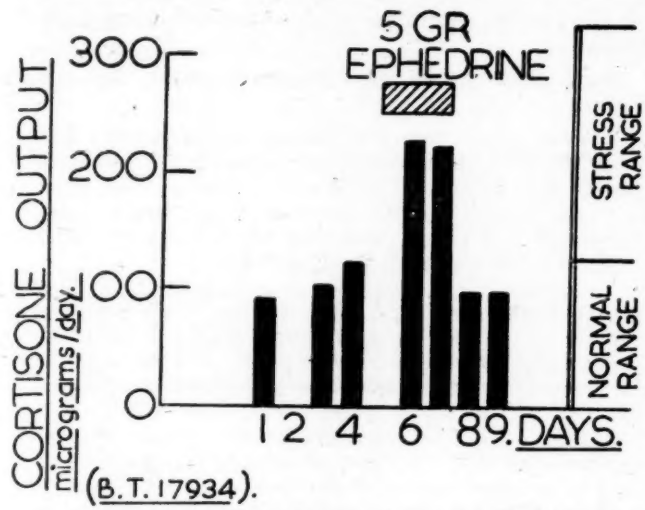


FIG. 5.—Effect of oral ephedrine on endogenous cortisone output.

of the adrenal cortex may have been due to the preceding infection, but such a conclusion should not be drawn from a single case.

Effect of Ephedrine

It is now well recognized, from experimental evidence in animals and from indirect evidence in man, that adrenaline acts as a potent stimulant to adrenal cortical function. Whether this is a specific effect or whether adrenaline merely represents another type of noxious stimulus or stress is at present undecided. Elsewhere (Cope and Bain, 1951) we have shown that continued adrenaline injection provokes an increase in the chemically determined neutral reducing steroids in the urine. Ephedrine acts similarly as an adrenal cortical stimulant. It can be used as an alternative to adrenaline in the eosinophil depression test in man (Abelson and Moyes, 1950). That it can also increase the actual output of cortisone in the urine is shown in the chart of B.T. (Fig. 5). This patient, who complained of anxiety type symptoms, was given 1 gr. (65 mg.) of ephedrine orally three times a day for five doses, after which he complained of symptoms suggesting overdosage, and the drug had to be stopped. A doubling of the cortisone output was observed during the period of administration, and there was a prompt return to normal on withdrawal of the ephedrine.

In view of this stimulant action of ephedrine it was of interest to determine whether this drug could be used to maintain in hyperactive state an adrenal cortex which had previously been stimulated to hyperactivity by A.C.T.H. Fig. 6 shows the result of such an experiment. The patient (N.S.) was suffering from fairly severe ulcerative colitis and received 100 mg. of A.C.T.H. daily for six days. There was a big increase in the cortisone output, which on the sixth day was estimated to be more than 650 μg.—a figure more than ten times the initial level of output. A.C.T.H. was stopped at this point, and ephedrine, ¼ gr. (32 mg.) three times a day, was continued by mouth for the next 12 days. At the end of this time a fresh determination showed that cortisone output had again fallen to normal levels. Ephedrine therefore failed to maintain the intense adrenal stimulation induced by A.C.T.H. Three weeks later a non-specific stress arose when peritonitis developed, and this provoked an increase in cortisone output greater than ephedrine had achieved.

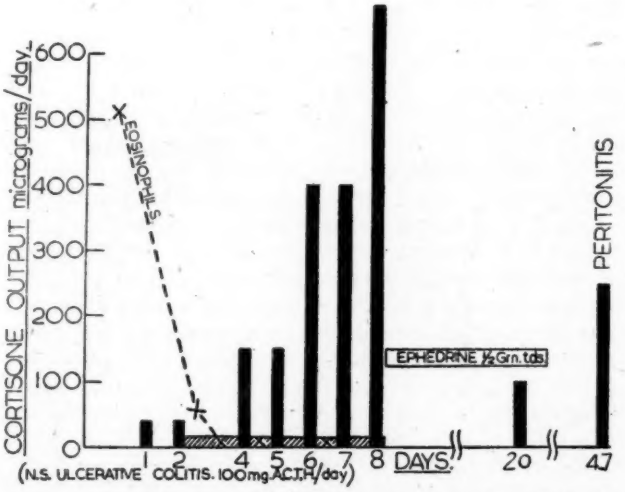


FIG. 6.—Good response to A.C.T.H. and failure of ephedrine to maintain the raised cortisone output.

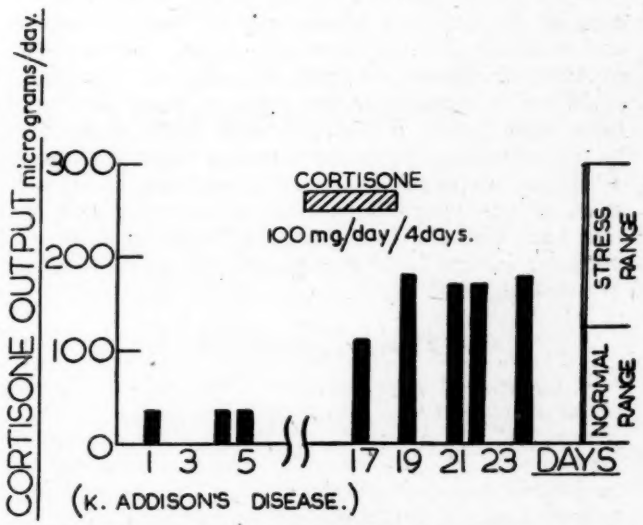


FIG. 7.—Effect of cortisone acetate injection on excretion of urinary cortisone.

Effects of Cortisone Therapy

With the mouse bio-assay method a rise in cortisone output in the urine can readily be detected in the 24 hours following a single intramuscular injection of cortisone acetate (Fig. 7). The excretion is very small compared with the dose given and does not represent more than 0.2%. The accompanying Table shows some typical

Table Showing Some Typical Rises in Cortisone Output in Cases of Adrenal Insufficiency after Cortisone Therapy

Case	Cortisone Output (μg./daily)			
	Output Before Treatment	Dose of Injected Cortisone (mg.)	Output After Last Injection	
			Days After	Amount
F. Hypopituitarism	<30	200 I.M.	1	180
			7	125
C. Hypopituitarism	50	50 (oral)	1	190
H. Addison's disease	70	50 × 10 I.M.	1	290
K. Addison's disease	<30	100 × 4 I.M.	1	180
			6	180

rises in cortisone output observed after cortisone therapy in varying dosage to persons with adrenal insufficiency. Three main points emerge from these figures. First, the rise in cortisone output after average therapeutic doses is in general less than occurs after similar therapeutic doses of A.C.T.H. This may not always be so, however, for all the cases included in this table were suffering from adrenal insufficiency. It is possible that higher outputs may be found when cortisone therapy is added to the production of a normal adrenal cortex in normal persons. Secondly, in two instances the rise in cortisone output persisted with little diminution for six or seven days after the last injection. This effect is presumably to be attributed to the slow absorption of this relatively insoluble substance from the depot produced at the injection sites. Thirdly, a prompt rise in cortisone excretion was observed in one case in the 24 hours following a small oral dose of cortisone acetate, thus providing objective confirmation of the clinical impression that cortisone is well absorbed when given by mouth.

Cortisone Output in Adrenal Insufficiency

A lowered output of cortisone in the urine is to be expected in Addison's disease and in hypopituitarism, and is usually but not invariably found. Seven cases of Addison's disease have been investigated. Cortisone could not be detected in the urine of three. In three other cases traces of activity were found, estimated as not exceeding 40 μg. daily, and in the seventh case a normal output of 70 μg. a day was assayed. Four cases of panhypopituitarism of varying severity have also been studied. In the urine of three of these no cortisone activity could be detected, but the fourth case excreted about 50 μg. a day.

Medical Stress in Adrenal Insufficiency

In one case of hypopituitarism the opportunity arose of observing cortisone output during a period of stress. The patient was suffering from the typical syndrome of post-partum pituitary necrosis. She was admitted to hospital in deep hypoglycaemic coma. In the 48 hours following recovery of consciousness the cortisone output did not exceed 40 μg. daily—a figure less than 25% of what might be expected after a comparable stress in a person with normally reacting adrenals. During a quiescent period ten days later no cortisone activity could be detected. Subsequently, after adrenal stimulation by 150 mg. of A.C.T.H. a cortisone output of about 150 μg. was observed, and a similar raised output resulted when cortisone was injected intramuscularly, showing that the low outputs at rest and during stress were not due to any inability of the kidney to excrete the hormone.

Discussion

It is concluded that the method of bio-assay of cortisone and compound F in urine which we have developed is sufficiently reliable, even when only three mice are used for each assay, to reveal the more gross variations in cortisone output in man. With larger numbers of mice in each group a higher accuracy would no doubt be obtained, but larger quantities of urine would be required for each assay. The technique we have used has necessitated for each assay urine collected over from 12 to 48 hours, according to the cortisone concentration present.

Four main ranges of cortisone excretion can be defined :

1. A low output, from 0 to 50 μg. a day, is usually found in conditions of adrenal inadequacy due either to Addison's disease or to panhypopituitarism.

2. The normal resting range lies, in our small series, between 40 and 120 μg., and these figures are very similar to those found earlier by Venning (1945).

3. A higher output is encountered in states of medical and probably other stress. The range then lies between 170 and 320 μg. a day. Outputs in this stress range are also found in the eighth month of normal pregnancy, and they can also be produced by oral ephedrine, or by intramuscular or oral cortisone acetate.

4. Finally, artificial stimulation of the adrenal cortex by intramuscular A.C.T.H. will, in suitably reactive subjects, lead to excessive outputs of cortisone—from 300 to 650 μg. a day, and probably even higher. Such outputs appear to be well above those encountered in medical stress. This range of high outputs of cortisone may therefore be called the "A.C.T.H. range."

An assay of the type here discussed has two main advantages over a study of the circulating eosinophils of the human subject. First, a moderate rise in cortisone excretion such as occurs in the first day of A.C.T.H. therapy is often sufficient to send the circulating eosinophils down to zero. Thereafter, further increases in cortisone excretion cannot be revealed by the eosinophils. Secondly, there is evidence that the changes in the circulating eosinophil cells do not necessarily reflect the cortisone output. Thus eosinophils reappeared in the blood of patient A.T. (Fig. 3) on the sixth day of A.C.T.H. therapy, when his observed cortisone excretion was at its maximum. We have also recently observed a patient with ulcerative colitis whose cortisone output rose under A.C.T.H. therapy to over 300 μg. a day, but whose eosinophil cells never fell below 100 per c.mm. and were often much higher. This lack of reliability of the eosinophil depression as an indicator of adrenal cortical stimulation in the human subject has also been noted by Posey, Mathieson, Mason, and Bargen (1950) in similar cases of ulcerative colitis. In their patients there was no satisfactory relation between adrenal corticoid output determined by a chemical method and the eosinophil drop.

Another method of following changes in adrenal cortical function now widely used is the chemical measurement of the daily output in the urine of the so-called adrenal corticoids. These are extracted by varying procedures in different laboratories and are usually estimated either by their reducing power towards sugar reagents or by their ability to produce formaldehyde on suitable oxidation. We have determined the reducing power towards Nelson's sugar reagent of a few extracts which had also been assayed for cortisone in adrenalectomized mice, and no parallelism between the two results has been apparent except after gross stimulation of the adrenal cortex by A.C.T.H. In late normal pregnancy, for instance, the cortisone output has always been found to be above normal although the total neutral reducing steroids determined chemically remain within normal limits. At least 90% of the total neutral reducing steroid present in such pregnancy urine is biologically inactive. Wick, Pecka, and Medz (1950) have come to a similar conclusion.

The cortisone excretions we have observed may not represent the whole amounts originally present in the urines, as some may well be lost or destroyed in the process of extraction (Paterson, Cox, and Marrian, 1950). Nevertheless, until more reliable methods of extraction are developed we believe that much useful information can be obtained by the bio-assay of such extracts.

Summary

The combined cortisone and compound F content of human urine has been measured by bio-assay. In resting normals the output ranges from 40 to 120 μg. daily.

In many types of stress due to medical disease the output is raised. The stress output ranges from 160 to 320 μg. a day. The output of cortisone-like hormone is raised in late normal pregnancy. A progressive rise in output occurs during A.C.T.H. therapy, when maximum outputs of over 600 μg. daily have been observed. The response to A.C.T.H. varies in different persons.

Ephedrine increases the output of cortisone-like hormone in the urine. It is unable to maintain adrenaline stimulation induced by A.C.T.H.

After cortisone, either injected or by mouth, a rise in output in the urine occurs, and may persist for at least a week after the last injection.

Excretion of cortisone-like hormone is usually reduced in Addison's disease and in panhypopituitarism.

The increased output of cortisone which medical stress normally provokes did not occur in a case of panhypopituitarism subjected to stress.

REFERENCES

Abelson, D., and Moyes, E. N. (1950). *Lancet*, **2**, 50.
Cope, C. L. (1951). *British Medical Journal*, **1**, 271.
—— and Bain, M. (1951). *Clin. Sci.*, **10**, 161.
Paterson, J. Y. F., Cox, R. I., and Marrian, G. F. (1950). *Biochem. J.*, **46**, xxix.
Posey, E. L., Mathieson, D. R., Mason, H. L., and Bargen, J. A. (1950). *Amer. J. med. Sci.*, **219**, 651.
Randolph, T. G. (1944). *J. Allergy*, **15**, 89.
Schneider, J. J. (1950). *J. biol. Chem.*, **183**, 365.
Venning, E. H. (1945). Transactions of Tenth Conference on Metabolic Aspects of Convalescence. Josiah Macy, Jun., Foundation, New York, 177.
—— Kazmin, V. E., and Bell, J. C. (1946). *Endocrinology*, **38**, 79.
Wick, A. N., Pecka, E., and Medz, R. (1950). *J. clin. Endocrinol.*, **10**, 84.
Zaffaroni, A., Burton, R. B., and Keutmann, E. H. (1950). *Science*, **111**, 6.

TRIALS OF ORAL STREPTOMYCIN FOR INFANTS WITH NON-SPECIFIC GASTROENTERITIS

Previous papers concerning the treatment of infantile gastroenteritis by streptomycin have reported contradictory results. James, Kramer, and Armitage (1948), recording the treatment of 30 infants, concluded that the course of the disease was materially shortened by streptomycin given by mouth; they used a total dosage of 2 g. over a period of seven days. They qualified this conclusion by the observation that many of their cases were infected with *Proteus vulgaris* and that it was not expected that all types of gastroenteritis would respond so well. Pulaski and Seeley (1948), and Leisti (1947) have also reported favourable results from treatment with oral streptomycin and Goettsch, Cobley, and Mulloy (1948) from combined treatment by the oral and intramuscular routes. None of these authors had a comparable series of control cases under observation during the period of their investigations.

On the other hand, Holzel, Martyn, and Apter (1949), in a carefully controlled study of the value of streptomycin in non-specific infantile diarrhoea and vomiting, were unable to demonstrate that the drug was an effective therapeutic agent. They gave some cases oral and some cases intramuscular streptomycin in similar amounts to those used by James *et al.* They record an impression that certain of their patients appeared to benefit, judged by the rate of clinical improvement. However, clinical and bacteriological observations failed to give either statistical evidence that the drug was of value or indications for its use.

The following papers report two independent clinical trials of the oral administration of streptomycin to infants suffering from non-specific gastroenteritis in which similar results have been obtained. They were carried out in centres in Edinburgh and London respectively.

I. TRIAL AT THE CITY HOSPITAL, EDINBURGH

BY

GLENYS M. LOWDON, M.B., Ch.B., M.R.C.P.

AND

MARGARET M. McNEILL, B.Sc.

(From the Department of Child Life and Health, University of Edinburgh)

In the gastroenteritis unit at the City Hospital in Edinburgh a trial of streptomycin therapy in non-specific gastroenteritis has been carried out by treating 24 cases with streptomycin and comparing the results with a concurrent control series.

The 48 cases here reported represent about half the cases treated in the unit during the period November, 1948, to January, 1950; very mild cases and cases treated with other oral antibiotics were excluded. In other respects the streptomycin-treated cases were "unselected." They were, in fact, nominated for streptomycin treatment on admission in rotation with control cases and cases treated with other antibiotics. The control cases were in the same way originally "unselected," but the 24 controls here presented are chosen from the larger group of control cases, so that each trial case is balanced by a control case of approximately the same age, date of admission, and clinical severity of enteritis.

As no epidemic of gastroenteritis occurred during the period of the trial, all the cases were of endemic type. Most of the babies were admitted from their own homes, where the social conditions were poor; two cases were transferred from maternity units, and 15 came from institutions.

TABLE I.—*Streptomycin-treated Cases*

Case No.	Age in Mths.	Clinical Severity	Parenteral Infection on Admission	Drugs			Relapse	Days of Diarrhoea After Admission	Days to Clinical Recovery	Remarks
				Strept. Total Dose	Sulph.	Penic.				
T.1	1	Mild	—	6 g.	+	—	1	4	37	Mild relapse
T.2	½	,,	—	6 ,,	+	—	1	7	45	,, ,,
T.3	½	,,	—	6 ,,	—	—	—	9	23	
T.4	¾	,,	—	6 ,,	+	+	1	17	55	Severe relapse. Phlebitis
T.5	½	,,	U.R.T. inf.	6 ,,	—	+	—	8	25	
T.6	2	,,	—	24 ,,	—	—	—	4	16	
T.7	3	,,	Ac. otit. med.	6 ,,	—	+	—	4	14	
T.8	4	,,	—	6 ,,	+	+	1	3	20	Mild relapse. Developed respiratory infection
T.9	2	,,	—	24 ,,	—	+	—	9	22	Developed respiratory infection
T.10	6	,,	—	6 ,,	—	—	—	4	10	
T.11	5	,,	—	6 ,,	+	—	—	11	18	Developed respiratory infection
T.12	5	,,	Bronchitis	6 ,,	+	—	1	5	57	Mild relapse
T.13	6	,,	Pharyngitis	24 ,,	+	—	—	12	19	
T.14	10	,,	Pur. conjunct.	24 ,,	—	—	—	4	16	
T.15	6	,,	—	6 ,,	—	—	1	9	35	Mild relapse treated with streptomycin
T.16	8	,,	...	24 ,,	—	—	—	4	14	
T.17	6½	Severe	—	24 ,,	—	—	1	10	31	Mild relapse
T.18	1	,,	—	24 ,,	+	—	1	17	29	,, ,,
T.19	5	,,	—	6 ,,	—	—	—	4	19	
T.20	2	,,	—	24 ,,	+	—	1	9	33	Phlebitis. Mild relapse
T.21	5	,,	U.R.T. inf.	24 ,,	+	—	—	11	24	Phlebitis
T.22	2	,,	(Foll. br. pneum.)	24 ,,	+	—	1	4	46	Mild relapse
T.23	7	,,	Bronchitis	6 ,,	+	—	—	8	24	
T.24	12	,,	Pharyngitis	6 ,,	—	+	—	3	6	

TABLE II.—*Control Cases*

Case No.	Age in Mths.	Clinical Severity	Parenteral Infection on Admission	Drugs			Relapse	Days of Diarrhoea After Admission	Days to Clinical Recovery	Remarks
				Strepto.	Sulph.	Penic.				
C.1	½	Mild	—	—	+	—	—	4	25	
C.2	½	,,	—	—	+	—	—	3	41	
C.3	½	,,	—	—	—	+	—	15	20	
C.4	1	,,	—	—	+	—	2	7	54	Mild relapses
C.5	1	,,	U.R.T. inf.	—	—	—	—	3	17	
C.6	2	,,	—	—	+	—	1	17	45	Mild relapse
C.7	3	,,	—	—	—	—	—	6	17	
C.8	3	,,	—	—	—	—	—	3	15	
C.9	3	,,	—	—	+	+	1	6	24	Mild relapse. Developed bronchitis
C.10	4	,,	—	—	—	+	—	13	19	Developed respiratory infection
C.11	5	,,	—	—	+	—	1	11	20	Became severe day 8
C.12	6	,,	Bronchitis	—	+	—	—	6	32	
C.13	6	,,	—	—	+	—	—	6	17	
C.14	7	,,	Dis. otit. med.	—	—	+	—	3	10	
C.15	8	,,	Bronchitis	—	+	—	1	11	30	Mild relapse
C.16	11	,,	—	—	+	+	1	17	33	Became severe day 12. Phlebitis
C.17	3	Severe	—	—	+	—	1	5	29	Mild relapse. Developed respiratory infection
C.18	3½	,,	—	—	+	—	1	9	46	Mild relapse
C.19	5	,,	—	—	+	+	1	11	36	Mild relapse. Phlebitis
C.20	5	,,	—	—	+	+	—	7	17	Developed otitis media
C.21	5	,,	—	—	+	+	—	11	20	Phlebitis
C.22	5	,,	Ulcerated skin	—	+	+	—	4	17	
C.23	7	,,	—	—	+	+	1	4	32	Mild relapse. Phlebitis
C.24	11	,,	—	—	+	—	—	4	10	

The babies had been artificially fed before admission, with one exception which was in the trial series.

All the babies were under 13 months of age. The series is too small for classification into age groups, but the ages of the children are shown in Tables I and II.

Parenteral Infection.—Eight trial cases had parenteral infections on admission: six had mild respiratory infections, one had a suppurative otitis media, and one a purulent conjunctivitis. Three trial cases developed upper respiratory infections while in hospital, and three had phlebitis. Five control cases had parenteral infections on admission; three had respiratory infections, one had a suppurative otitis media, and one had skin sepsis. Three control cases developed upper respiratory infections while in hospital, one developed an otitis media, and five had phlebitis.

Severity of Illness.—The assessment of the severity of the disease before treatment is necessarily a purely clinical one; cases have been categorized as "severe" if intravenous therapy was required within 24 hours of admission, and "mild" if not.

Treatment

Routine treatment was similar in all cases, and consisted, in the "mild" cases, of 24 to 36 hours' oral half-strength Ringer lactate solution and 5% glucose, preceded by gastric lavage, and followed by graduated milk feeding with a half-cream dried milk. Potassium chloride, 1 g., was added daily to the feeds until half-strength milk feeds were given.

In the "severe" cases oral feeding was withheld for 24 to 36 hours and half-strength Ringer lactate solution with 5% glucose was given intravenously. After dehydration was corrected 1 g. of potassium chloride was added to each 24 hours' intravenous fluid. Oral feeding with a half-cream dried milk was gradually established.

Vitamin C (oral or intravenous) and the total vitamin B complex (oral or intramuscular) were given daily.

Streptomycin Therapy.—All the trial cases received oral streptomycin initially; 14 cases were given 1 g. daily in divided doses for six days, and 10 cases were given 2 g. daily in divided doses for 12 days (see Table I).

Other Drug Therapy.—In the trial series, 12 babies received sulphadiazine; in four cases this was given with streptomycin on account of respiratory infection present on admission, and in eight it was given later—for respiratory infection in one case, and because of relapse of gastroenteritis in seven cases. This change of therapy for the relapses in the trial series was based on the

considerations that organisms present in the stools of the infants after streptomycin therapy were predominantly streptomycin-resistant, and that these patients might have some undetected parenteral infection.

In the control series, 18 received sulphadiazine either on admission or subsequently.

Penicillin was given by intramuscular injection to six of the trial cases (parenteral infection, 5; phlebitis, 1), and to 10 of the control cases (parenteral infection, 4; phlebitis, 5; prophylactic, 1).

Results

As the return of some of the babies to their own homes was delayed for social reasons after recovery from gastroenteritis, the total number of days in hospital for each patient has not been used in assessing the results of treatment.

The number of days to "full clinical recovery" has been chosen as a more reliable measure. An infant was considered to have reached this stage when full feeds were being tolerated and the stools and weight were satisfactory. The number of days of diarrhoea in each case has also been recorded; for this purpose the first of at least three consecutive days of normal stools has been regarded as marking the end of diarrhoea.

Details of the individual cases in the trial and control series are shown in Tables I and II. Comparison of these series (Table III) in respect of average number of

TABLE III.—*Comparison of Results of Treatment in Control and Trial Series*

	No. of Cases	Days of Diarrhoea	Days to Full Clinical Recovery	Relapse	
				Mild	Severe
Mild {Trials	16	7·1	26·6	5	1
Mild {Controls	16	8·2	26·2	4	2
Severe {Trials	8	8·3	26·5	4	0
Severe {Controls	8	6·9	25·9	4	0
All cases {Trials	24	7·5	26·6	9	1
All cases {Controls	24	7·8	26·1	8	2
Trial cases treated by strept. 2 g. daily for 12 days	10	8·4	25·0	3	0
Corresponding control cases	10	8·5	25·8	4	0

days to full clinical recovery (26.6 and 26.1 days respectively), average number of days of diarrhoea (7.5 and 7.8 days), and relapse rate (10 in each group) shows remarkable similarity. There were no deaths. In Table III the results are classified into mild and severe groups; as the possible effect of the higher dose of streptomycin is of interest, the results in the 10 cases so treated are also shown separately.

The results have been examined statistically by Dr. Woolf, of the Department of Social Medicine of Edinburgh University, who finds that the differences observed are not significant.

Bacteriology

Rectal swabs were taken on admission and daily thereafter. The daily swabs were continued for two weeks or more in all patients except four trial cases and three control cases, in which they were obtained for a shorter period (4–10 days). The first three swabs were cultured on special media to exclude known pathogens. Thereafter a MacConkey plate was inoculated for observation of *Bact. coli* and enterococci. Christensen's urea medium was used for identification of *Proteus*.

TABLE IV.—*Bacteriological Studies of Streptomycin-treated Cases*

Case No.	No. of Rectal Swabs	Days on Strept.	Before Treatment			Days of No Growth	Days Free From		
			Bact. coli	Ent.	*Prot.*		*Bact. coli*	Ent.	*Prot.*
T.1	13	6	+	+	+	1	12	1	12+
T.2	14	6	+	+	−	0	8	0	—
T.3	14	6	+	+	−	2	8	6	—
T.4	14+	6	+	+	−	2	9	3	—
T.5	14	6	+	+	−	4	10	4	—
T.6	14	12	+	−	+	9	13+	9	13+
T.7	14	6	+	+	+	7	9	7	13+
T.8	14	6	+	−	−	1	1	2	—
T.9	9	12	+	+	−	1	1	1	—
T.10	14	6	+	+	−	4	9	4	—
T.11	14	6	+	+	+	0	0	7	12
T.12	14	6	+	+	+	0	0	4	8
T.13	4	12	+	+	−	0	2	0	—
T.14	14	12	+	−	+	6	6	7	13+
T.15	14+	6	−	+	+	1	2	1	2
T.16	14	12	−	+	+	0	4	0	12+
T.17	13	12	+	+	+	0	0	1	12+
T.18	14+	12	+	+	−	0	1	0	—
T.19	14	6	+	−	+	1	1	2	9
T.20	14	12	+	+	+	9	9	13+	13+
T.21	9	12	+	+	−	3	3	3	—
T.22	14	12	+	+	+	3	3	3	13+
T.23	14+	6	+	+	−	0	4	0	—
T.24	7	6	+	+	+	0	2	0	2

Serological examination of *Bact. coli* was carried out on admission in 20 of the trial cases and in 22 of the control cases. The alpha strain of *Bact. coli* was isolated in six of the trial cases and in 10 of the controls.

In the majority of the trial cases no growth from the rectal swab was obtained for a variable number of days (Table IV). No correlation is apparent between the time during which organisms were absent from the stool and the rate of clinical progress. In the control cases no diminution in the bacterial flora was observed by the techniques employed.

Proteus was present on admission in 13 of the trial cases and disappeared for two days or more in all of these. It will be seen from Table IV that the higher dose of streptomycin used in 10 cases appeared to be more effective in clearing the stool of this organism. Seven patients with *Proteus* received the smaller dose of streptomycin; return of *Proteus* to the stool was observed during the six-days course in two and after completion of the course in three. In six patients with *Proteus* on admission who received the larger dose, no return of that organism was observed, but in these cases daily swabs were taken for only two days after completion of the 12-day course of streptomycin. In the control group *Proteus* was present on admission in 12 patients: nine of them showed temporary clearance of the organism, and four of these were free of *Proteus* for 10 or more consecutive days. In these cases no relation could be observed between the presence of *Proteus* and severity or duration of gastroenteritis.

Sensitivity plates incorporating 10, 50, and 100 units of streptomycin per ml. of MacConkey medium were set up daily in 19 of the trial cases. With a concentration of 50 units per ml. all growth from swabs taken before streptomycin treatment was inhibited in all but two cases. Streptomycin-resistant strains of *Bact. coli* and enterococci appeared later in all these cases at times varying from 1 to 13 days after starting oral streptomycin.

Conclusion

Until the cause of non-specific gastroenteritis is known the assessment of any new therapy must be clinical and be based on comparison with a concurrent control series.

Sulphadiazine was given to most of our control cases because this has been our routine practice, based on

the opinion that this drug assists the recovery from gastroenteritis even if only by its effect in reducing secondary infection.

From this trial of oral streptomycin it must be concluded that the drug did not influence the course of the disease any more or any less favourably than the treatment given to the control group. Streptomycin given by mouth has the disadvantages that it readily produces resistant strains of organisms and that, not being absorbed, it does not incidentally control secondary infection. There appears, therefore, to be no reason to prefer oral streptomycin to sulphadiazine in the treatment of non-specific gastroenteritis.

Summary

From the gastroenteritis unit in Edinburgh 24 cases of non-specific infantile gastroenteritis treated with oral streptomycin are compared with a control series receiving no oral antibiotics. Clinical and bacteriological studies are reported. The streptomycin-treated cases did not show better clinical progress than the control cases.

The authors wish to acknowledge indebtedness to Dr. A. Joe and Professor R. W. B. Ellis for facilities and for help in this study, and to Dr. J. Smith, of Aberdeen, for assistance with the serological examination of *Bact. coli*.

II. TRIALS AT THE QUEEN ELIZABETH HOSPITAL, HACKNEY

BY

WINIFRED F. YOUNG, M.A., M.D.

GWEN SMITH, M.B., B.S., D.C.H.

ALEX RUSSELL, O.B.E., M.R.C.P., B.Hyg., D.P.H. D.C.H.

AND

B. McNICHOLL, M.D., M.R.C.P., D.C.H.

(From the Queen Elizabeth Hospital for Children, Hackney)

The subjects for investigation were patients under 1 year of age admitted to a cubicle ward reserved for infants with gastroenteritis. Those patients who were judged to be suffering from gastroenteritis as the primary disease, whether evidence of parenteral infection was present or not, were included in the investigation. Patients who developed gastroenteritis at a time when they were suffering from other diseases or who had diarrhoea and vomiting as a symptom of some other disease were excluded from the controlled trials. Other cases admitted to the ward but omitted from the results were those with a history of diarrhoea preceding admission but with no diarrhoea in hospital, and those with diarrhoea due to *Shigella* or *Salmonella* infections.

The Investigation

Preliminary trials were made on small numbers of cases between August, 1947, and January, 1949, but the results were inconclusive. However, valuable experience was gained and methods were devised for assessing the response of infants with gastroenteritis to a therapeutic agent. These were applied to the main investigation, which took place during a thirteen-months period from January, 1949, to February, 1950. The cases were subdivided into groups according to severity and age before allocating them to the trial and control series. The dosage of streptomycin was usually 5 g. in 15 days, given in divided doses at four-hourly intervals, but a shorter course was given to cases which improved rapidly.

Ninety-seven infants were included in the investigation. A detailed study of the source of infection in these patients has not been made, but 30 were transferred from hospital wards or residential nurseries or had been inmates therein within a week of the onset of their diarrhoea.

Grouping.—The patients were grouped as follows: (1) According to severity: severe (S) cases were those which received intravenous infusions within the first 24 hours after admission, and mild (M) cases were those which received their entire fluid intake by mouth during this period. (2) According to age: Group I, 0–2 months; Group II, 2–6 months; Group III, 6–12 months.

The infants were grouped within 24 hours of admission, alternate cases within each age group and within the classes M and S being allocated to the streptomycin trial and to the control series. The number of cases in each group is shown in Table I. Of the 97 cases 40 were classed as severe and 57 as mild. The results from the three age groups were analysed together, as the numbers were too small for separate assessment and there were no obvious differences between the progress of the younger and the older babies.

TABLE I.—*Number of Cases. Grouping According to Severity and Age in Streptomycin Trial and Control Series. (Two Group II Controls Received Streptomycin Late in the Course of Their Disease; They Have Been Included in the Analysis of the Results)*

Groups		I Aged 0–2 mths.	II Aged 3–6 mths.	III Aged 7–12 mths.	Total
Mild	Trial	7	12	7	26
	Control	9	12	10	31
Severe	Trial	5	10	3	18
	Control	7	10 + 2	3	20 + 2
Total		28	44 + 2	23	95 + 2

Feeding and Fluid Administration

Milk feeds were introduced after tolerance for fluids by mouth had been established for 24 hours. These were given even if diarrhoea had persisted, but not if vomiting and abdominal distension were present. In mild cases glucose and electrolyte solutions (in this paper referred to as clear fluids) were given by mouth for the first 24 hours. On the second day milk mixture to supply 10 cals./lb. body weight was offered, and the amount was then increased by 10 cals./lb daily. The severe cases were given nothing but sips of fluid by mouth during the initial 24-hour period while rehydration was being achieved by means of intravenous infusions. On the second day clear fluids were given by mouth to supply one-third of the total fluid requirements, the other two-thirds being given by the intravenous route; on the third day diluted milk feeds were introduced to supply 10 cals./lb. body weight of milk mixture and two-thirds of the total fluid requirements. On the fourth day full fluid requirements by mouth were prescribed and the intake of milk mixture was increased to supply 20 cals./lb. body weight, while on the fifth day the intake of milk mixture was increased to 30 cals./lb. body weight. Failure to tolerate this feeding regime was regarded as evidence that the gastroenteritis had not been controlled, and the feeds were regraded, starting with clear fluids.

Patients receiving the whole of their fluid intake by mouth were given vitamin supplements (B complex and C) orally, while those receiving intravenous infusions were given them by injection. Vitamin K was also given to these patients. Vitamins A and D were added as soon as tolerance to feeding was established.

Parenteral Infection

Table II shows the incidence of parenteral infection, (1) at the time of admission and (2) later in their hospital course, among the patients in the two series. It can be seen that approximately the same number of infants were affected at the time of admission in the streptomycin trial and in the control series. At the later stage, the incidence of infections resulting from intravenous infusions (usually mild phlebitis) was somewhat higher in the control series. All infections in either series were treated with sulphonamides or with penicillin as considered necessary on clinical or bacteriological grounds. Table II also shows the numbers of infants who received such special therapy. Apart from the complications of intravenous therapy, it may be assumed that parenteral infections have affected progress to a similar extent in the two series. Since the intravenous complications were never of such severity as to delay the date of clinical recovery, it is believed that the higher incidence of intravenous complications in the control series has not affected the assessment of the results to be described.

TABLE II.—*Incidence of Parenteral Infection and Number of Patients Receiving Special Treatment (Sulphonamide Drugs and Penicillin) Among the Streptomycin Trial and Control Series*

Groups		No. of Cases	Parenteral Infection				
			On Admission		Later		
			Total	Special Treatment	Due to Intravenous Complications	Other Infections	Special Treatment
Mild	Trial	26	10	7	1	4	4
	Control	31	16	9	1	3	4
Severe	Trial	18	9	6	6	3	8
	Control	22	8	6	12	5	14
Total		97	43	28	20	15	30

Clinical Observations

Mortality Rate

There were three deaths among 98 infants; one occurred within two hours of admission and this case has been omitted. The other two patients who died were: (i) a control case with a congenital heart lesion, who succumbed very rapidly to the disease with evidence of cardiac failure in the terminal stage; (ii) a young prematurely born infant in the streptomycin trial series, who died during a severe relapse judged to be due to infection acquired from his mother.

The mortality from uncomplicated infantile gastroenteritis has become low in well-equipped and well-staffed wards, and therefore assessment of the value of a therapeutic agent cannot be based upon the number of deaths.

Progress

The following criteria have been used to compare the clinical course in the streptomycin trial and in the control series: (i) duration of diarrhoea; (ii) duration to "clinical recovery"; (iii) incidence of relapses; (iv) tolerance of food.

(i) The duration of diarrhoea was assessed from the nurses' records and from daily examination of the stools.

(ii) "Clinical recovery" denotes the time when a patient was considered fit for discharge, although it was not always synonymous with length of hospital stay. This was frequently extended owing to social difficulties which delayed discharge.

(iii) Increase in the severity and the recurrence of diarrhoea, whether due to exacerbations or to acquired infection, have been termed relapses, since there is no method of differentiating between them. They have been classed as mild or severe (assessed by the same criteria as the state on admission), and those occurring before and after clinical recovery have been tabulated separately.

(iv) Since milk was offered early in the course of treatment, the number of patients who were able to tolerate it at this stage could be used as a basis of comparison. Intolerance evidenced by vomiting, abdominal distension, or exacerbation of the diarrhoea was apparent in some cases, and then clear fluids were substituted for a further period. This has been termed regrading of the feeds. Tolerance of milk feeds was assessed in further detail by subdividing the cases according to the number of days after admission when milk was introduced without subsequent regrading of the feeds. Tolerance of full feeds was assessed in a similar way, a calorie intake of 50 cals./lb. in 24 hours being the amount chosen to indicate full feeding.

The data relating to duration of diarrhoea, clinical recovery, and relapses have been summarized in Table III. Among the severe cases diarrhoea was controlled by the fourteenth day in 15 out of 22 in the control series and in 14 out of 18 in the streptomycin cases. Fifteen out of 22 controls and 14 out of 18 trial cases were considered convalescent by the twenty-first day. There is therefore little apparent difference in the progress of the two groups. It should be noted, however, that diarrhoea was controlled early (within four days) in a higher proportion of the trial cases. The contrast is greater among the severe than among the mild cases, in whom untreated diarrhoea is likely to be of shorter duration. For the whole of each series (mild and severe cases), diarrhoea

TABLE III.—*Clinical Progress of Infants in the Streptomycin Trial and Control Series. The Death in the Control Series Occurred before Diarrhoea had been Controlled, and therefore there are no Data for this Case. The One in the Trial Series Occurred after a Late Relapse, and the Data for the First Illness have been Included. In the Relapse Column, B = Before Clinical Recovery and A = a Later Stage*

Group		No. of Cases	Duration of Diarrhoea for Days After Admission						Relapses				Recovery Days After Admission						Deaths
									Mild		Severe								
		97	0–4	5–7	8–10	11–14	15–21	21+	B	A	B	A	0–7	8–14	15–21	22–28	29–35	35+	
Mild	Trial	26	13	5	4	1	2	1	1	2	2	2	9	13	1	1		2	0
	Control	31	10	8	4	5	3	1	0	0	4	2	11	11	6	1	2		0
Severe	Trial	18	5	6	2	1	3	1	1	0	0	2	1	10	3	3	1	0	1
	Control	22	1	7	3	4	6	0	2	0	2	1	0	9	6	4	0	2	1

was controlled within four days in 18 out of 44 trial cases, compared with 11 of 52 control cases. This gives $\chi^2 = 4.41$, $0.02<P<0.05$, which implies a significant difference between the two series. The rate of clinical recovery was also a little better in the trial series.

The incidence of relapses is similar in the two groups. Among the mild cases 6 (2 trial and 4 control) became severe before clinical recovery and 4 (2 trial and 2 control) at a later stage. Among the severe cases there were 5 severe relapses (2 trial and 3 control cases); two of the relapses which occurred among the streptomycin trial cases began during the period that streptomycin was being given.

The comparison between tolerance of food in the streptomycin trial and in the control series is presented in Table IV. It will be seen that almost all of the mild cases were able to tolerate milk early, both in the trial and in the control series. However, in the severe cases a slightly higher proportion of those receiving streptomycin than of the controls tolerated food within four days of admission—15 among 19, as opposed to 11 out of 21. This difference in food tolerance is not apparent from the figures for full feeding, 13 out of 19 streptomycin-treated cases having reached full feeding by the fourteenth day as compared with 14 out of 21 among the control series. A somewhat higher proportion of control cases (12 out of 53) than of trial cases (7 out of 45) required regrading of the feeds. This observation is in accord with the data regarding duration of diarrhoea, rate of clinical recovery, and early tolerance of milk.

Bacteriology

Rectal swabs were taken at the time of admission and thereafter twice weekly. The follow-up swabs were obtained on the same two days of the week from all the inmates in the ward and consequently at varying intervals after the day of admission. The results have been summarized to show the bacteriology (*a*) at the time of admission, (*b*) at the two subsequent examinations, (*c*) at the third and fourth follow-up examinations. All the swabs included in this analysis were obtained within two weeks of admission and therefore during the course of streptomycin administration for the trial cases. The (*b*) and (*c*) groups of results are with few exceptions those from swabs taken during the first and second weeks respectively.

The bacteriological findings have been divided into (1) special type *Bact. coli* (α and β), (2) *Proteus (morgani* and *vulgaris)*, (3) other than *Bact. coli* organisms. The antisera required for the typing of the special strains of *Bact. coli* did not become available until after the investigation had been started—the α type two months and the β type not until ten months after the outset. The results for these organisms are therefore incomplete. Those for the β type are not shown in detail, as the number of swabs examined was very small in proportion to the total for the investigation. The antisera which were used were obtained from Dr. Joan Taylor, Salmonella Reference Laboratory, Colindale. The method employed was selection of four *Bact. coli* colonies for slide agglutination.

Table V(a) shows the incidence of the α strain in swabs taken from the streptomycin trial and control series. It can be seen that 30% of those taken at the time of admission were positive in the streptomycin trial, compared with 19% in the control series. They were distributed evenly among the severe and mild cases. At subsequent examinations the relative number of swabs showing the presence of α type was higher than in the admission swabs for both series, but the increase was greater among the streptomycin trial cases. The persistence (and at times fresh appearance) of this organism in swabs taken from patients receiving streptomycin is in accord with

TABLE IV.—*Tolerance of Food by the Streptomycin Trial and Control Series*

Group		No. of Cases	Diluted Milk Tolerated from Days After Admission					Feeds Regraded	Full Feeds Tolerated from Days After Admission					
			0–2	3–4	5–7	8–10	10+		0–7	8–14	15–21	22–28	29–35	35+
Mild	Trial	26	23	0	1	0	2	2	16	5	3	1		1
	Control	31	27	0	1	2	1	4	12	14	5			
Severe	Trial	18 with 1 death	8	6	1	0	3	5	2	10	4	1	1	
	Control	21 with 1 death	6	5	3	3	4	8	3	11	5	2		

TABLE V.—*The Bacteriology of Rectal Swabs in the Streptomycin Trial and Control Series*

Time	Streptomycin Trial				Control Series			
	(a) *Bact. coli*—α type							
	Total Swabs	Number Examined	Positive	% Positive	Total Swabs	Number Examined	Positive	% Positive
O.A.	48	33	10	30	53	36	7	19
1st period	96	77	40	52	106	83	19	23
2nd period	96	53	41	77	106	55	23	42

Time	(b) *Proteus* and other organisms															
	Total Swabs	Number Examined	Positive			% Positive			Total Swabs	Number Examined	Positive			% Positive		
			Prot.		Others	Prot.		Others			Prot.		Others	Prot.		Others
			M.	V.		M.	V.				M.	V.		M.	V.	
O.A.	48	42	4	0	6	10	0	14	53	43	9	6	6	21	14	14
1st period	96	94	2	1	7	2	1	6	106	99	28	18	7	28	18	7
2nd period	96	63	5	2	4	8	3	7	106	68	21	15	3	31	22	4

the findings reported by Holzel *et al.* (1949). In our cases the number of patients acquiring this organism was higher in the trial than in the control series. This finding is interesting in the light of the observation by Holzel *et al.* that streptomycin promotes the spread of resistant strains.

The small number of swabs examined for the β type *Bact. coli* showed a low incidence of this organism at the time of admission for both series, and it increased somewhat, as for the α type, in the swabs examined subsequently.

Table V(b) shows the incidence of the *Proteus* and other organisms. It can be seen that *P. morgani* and *P. vulgaris* were seldom found at the time of admission in swabs taken from the streptomycin trial series, but occurred more frequently in swabs from the control series. The effect of streptomycin on these organisms therefore cannot be assessed and compared with the results obtained by previous workers. The other organisms which were found included *Staph. albus*, enterococci, *Candida albicans*, *Bact. mucosus capulatus*, *Bact. faecalis alkaligenes*, *Bact. aerogenes*, *Ps. pyocyanea*, and the paracolon bacillus.

No attempt has been made to correlate the bacteriological findings with the clinical course of our patients. It has been noted, however, that one of the organisms belonging to the groups which have been studied has frequently appeared for the first time in the culture of a rectal swab taken when the patient was making good progress or had recovered without producing a relapse.

Discussion

Variations in the clinical course of cases suffering from infantile gastroenteritis make it difficult to assess the effects of special treatment. Many cases improved rapidly after simple regrading of the feeds, and any series which includes a high proportion of such cases is unsuitable for testing the value of a therapeutic agent. This point is well illustrated by the observations made by Holzel *et al.* Among 38 cases used for a controlled trial, 7 of which were classed as mild and 31 as of moderate severity, all the control cases and all but 3 of the trial cases recovered rapidly.

More significant observations were made by Holzel *et al.* from their series of 41 severe cases, of which 14 received oral and 16 intramuscular streptomycin, and 11 were controls. There were 14 deaths, of which 6 occurred in the oral and 5 in the intramuscular-streptomycin-treated groups, and 3 in the control groups. All of the survivors in the control group made rapid improvement, but improvement was delayed in 3 of those in the oral and in 8 of those in the intramuscular-streptomycin-treated groups. The mortality rates and progress of these patients indicate clearly that there was no benefit attributable to streptomycin among the majority of infants who received it.

The conclusion drawn from the Edinburgh trial recorded in the first part of this paper is in agreement. The clinical course of the gastroenteritis which was under review might have been expected to demonstrate a response to an effective therapeutic agent, since the average time for duration of diarrhoea and for recovery was 8 and 26 days respectively in the control group. Yet the results for the trial group showed no reduction of the average time for the duration of diarrhoea and recovery, and were almost identical with those for the control group.

In contrast, James *et al.* (1948) obtained a good response to streptomycin. The subjects for their investigation included 12 children who developed epidemic gastroenteritis of moderate severity in a residential nursery. There were eight control cases for whom the average recovery rate (gauged by the time to regain the greatest weight reached before the illness) was 31 days. The streptomycin-treated cases, which were of somewhat greater severity, had an average recovery rate of 11 days. This evidence suggesting a benefit from oral streptomycin is supported by similar results in an epidemic of neonatal diarrhoea, and also by a good response to streptomycin in 20 out of 22 infants admitted to a children's hospital with endemic gastroenteritis. All but three of the latter cases had previously failed to respond to routine treatment given for periods varying from 3 to 32 days, but there were no controls for this series.

The results of the present investigation may serve to correlate the differences between the findings of other workers. The progress of our mild cases was rapid in a high proportion of both the trial and the control series, but this was not as uniform as in the cases of Holzel *et al.* with mild or moderately severe gastroenteritis. The number of cases showing rapid improvement, evidenced by (i) diarrhoea lasting for four or less days, (ii) clinical recovery within two weeks, (iii) toleration of full milk feeds within a week, is slightly higher among the patients who received streptomycin; and among the severe cases the contrast between the results for the trial and the control series is somewhat greater than among the mild cases. This is best demonstrated by the figures for the duration of diarrhoea and those showing the number of cases which required regrading of their feeds. It must be appreciated, however, that when rapid improvement occurred it could be attributed to streptomycin only in a small number of cases receiving the drug, since many control cases made similar progress. Furthermore, many treated cases failed to respond to streptomycin, and clinical improvement was long delayed, while two had exacerbations of diarrhoea before the drug was discontinued. For instance, the duration of diarrhoea in 7 out of 19 severe and in 8 out of 26 mild streptomycin trial cases exceeded a week, while 8 and 4 cases respectively took longer than two weeks to reach the convalescent stage. Two mild cases became severe, despite the fact that they were receiving streptomycin. These results seem to show that streptomycin may have helped some patients but that for many it was completely ineffective. This finding is supported by the poor response to streptomycin of many of the patients who were observed during the second preliminary trial.

Bacteriological studies in this and in previous investigations have failed to supply a lead regarding the cases which might be likely to benefit from streptomycin administration. The persistence of organisms and the appearance of new flora in our patients receiving streptomycin might be taken as an indication that we were using too small a dose. This is unlikely, since the much larger dose used in the Edinburgh trial eliminated the flora of the faeces in a number of cases, but this change could not be correlated with an improved rate of clinical progress.

Since no consistent benefit from streptomycin has been demonstrated, there would seem to be little place for it in the routine treatment of gastroenteritis. Indications for its use might be the critical state of an individual patient or a severe epidemic in which the early cases were found to respond well.

The results of early trials with chloramphenicol (Rogers, Koegler, and Gerrard, 1949) suggest that it is an effective therapeutic agent in gastroenteritis. If its value is confirmed the use of streptomycin will be entirely superseded.

Summary

Trials of oral streptomycin for infants under 1 year suffering from endemic non-specific gastroenteritis extended in three stages over the period August, 1947, to February, 1950. The main stage of the investigation included 97 babies who were grouped according to age and to the severity of their disease, and alternate cases in each age group were allocated to the trial and control series.

No clear-cut response to streptomycin has been demonstrated, but the data on which clinical assessment was based show that there was slightly better progress among the streptomycin-treated cases and that the contrast was more marked among the severe cases. Many cases failed to respond to streptomycin, and it cannot be regarded as an effective therapeutic agent for the disease.

Bacteriological studies were made, but the results throw no light on the aetiology of gastroenteritis. Streptomycin in the dosage employed failed to eliminate the special type *Bact. coli*, alpha and beta.

We are grateful to Dr. R. H. Dobbs and Dr. I. M. Anderson for permission to study their cases and for their advice in the planning of the investigations. We are indebted to Dr. B. Levin for his help throughout the investigation and for the provision of the bacteriological data. We also wish to thank Mr. G. Hunt for his technical assistance in the bacteriological studies. Dr. Richard Doll has been kind enough to advise us about the statistical significance of the data.

REFERENCES

Goettsch, E., Cobley, G., and Mulloy, M. (1948). *Pediat.*, **2**, 1.
Holzel, A., Martyn, G., and Apter, L. (1949). *British Medical Journal*, **2**, 454.
James, U., Kramer, I. R. H., and Armitage, P. (1948). *Lancet*, **2**, 555.
Leisti, P. (1947). *Ann. Med., intern. fenn.*, **36**, 575.
Pulaski, E. J., and Seeley, S. F. (1948). *J. Lab. clin. Med.*, **33**, 1.
Rogers, K. B., Koegler, S. J., and Gerrard, John (1949). *British Medical Journal*, **2**, 1501.

Sir John Cockcroft said recently at Oxford that there are three scientific freedoms: freedom to work on any subject in science; freedom to publish results; and freedom to meet other scientists and discuss one's work fully with them. In this country, so far as the first is concerned, while university expenditure is more and more provided by Government funds, the money is administered by the University Grants Committee under a system which leaves them completely free to decide how they will spend it. The only exceptions are the large expenditures on research in nuclear physics and a few other special projects financed by the Department of Scientific and Industrial Research on the recommendation of expert committees. Outside the universities, in research conducted by the Medical Research Council or the Ministry of Supply, for example, a much greater element of planning is evident, because these departments have to work towards certain objectives, but even so probably 30%–50% of the work of the civil departments could be classed as fundamental and long-range research, and therefore not plannable. On the whole, therefore, Sir John thought that scientific freedom in this country is not imperilled by State planning. The second freedom, that of publication, is always subject to one important qualification —that results must not be published unless the worker is as sure of them as is reasonably possible. Secrecy has been retained to-day only in matters of technological importance, which hardly constitutes a restriction on freedom of science. In the Western world there are still fairly complete freedom of movement and a plethora of scientific conferences. But there are signs that this freedom may be subject to some restriction in the future, partly as a result of the passage in the United States of the Internal Security Act.

ON CHEMICAL TESTS FOR BLOOD IN URINE

BY

HAROLD CAPLAN, M.B., B.S.

AND

GEORGE DISCOMBE, M.D., B.Sc.

(From the Central Middlesex Hospital, Park Royal, London)

Chemical tests for haematuria are still used when a centrifuge and microscope are not available. Little information on their sensitivity is to be found. We therefore report on the absolute and relative sensitivity of the *ortho*tolidine hydrochloride, benzidine, Kastle–Meyer or reduced phenolphthalein, amidopyrine, and guaiac chemical tests, of direct spectroscopy, and of microscopy under standard conditions, and comment on their convenience and reliability.

Experimental

Urine.—The urine samples were prepared from blood (Hb, 14.3 g. per 100 ml., red cells, 5,000,000 per c.mm.) diluted with urine obtained from the same individual. Dilutions were made with fresh urine, urine which had stood for 24 hours to allow oxidation of ascorbic acid, and the same two urines to which had been added 2 mg. of ascorbic acid per 100 ml. This was done because Kohn and Watrous (1938), Barach and Pennock (1943), and Zwarenstein (1949) have found that an excess of ascorbic acid inhibits the benzidine and *o*-tolidine hydrochloride tests; and 2 mg. per 100 ml. represents an average normal concentration. It was found that fresh and stale urines gave the same results, but that ascorbic acid decreased the sensitivity of some tests. The sensitivity varied less than twofold among five replicate experiments.

Technique of Tests.—Most tests were performed as described by Harrison (1947), the *o*-tolidine hydrochloride test as described by Zwarenstein. Spectroscopy consisted in examining a 1-in. (2.5-cm.) layer for the bands of oxyhaemoglobin; it could be made about five times more sensitive by converting the haemoglobin to pyridine haemochromogen, and observing a 2-in. (5-cm.) layer, but this is not a suitable procedure for domiciliary work because of the smell. The centrifuged deposit was obtained by centrifuging 5 ml. at 3,000 rev./min., removing 4 ml. of supernatant, mixing the residue, and examining between slide and cover-slip or in a Fuchs–Rosenthal haemocytometer. The use of the haemocytometer renders the test ten times more sensitive. The sensitivity could be increased about five times more if the Addis technique (12.5 ml. at 3,000 rev./min.; remove 12 ml. and suspend in the residual 0.5 ml.) were used.

Two tests are noteworthy: one comparatively insensitive but simple, the other very sensitive and fairly simple; they are therefore described in detail.

Amidopyrine Test.—Reagents: 5% amidopyrine in 95% alcohol; 10-volume hydrogen peroxide. Acidify 3 ml. of urine with a few drops of acetic acid and overlay with 1–2 ml. of amidopyrine solution; allow 5 to 6 drops of hydrogen peroxide to fall through the alcoholic layer. Stand for a few minutes. A blue or lilac-coloured ring is a positive reaction.

Orthotolidine Hydrochloride Test (*Zwarenstein*).—Reagents: solid *o*-tolidine hydrochloride; a mixture of equal

volumes of glacial acetic acid and 10-volume hydrogen peroxide (acid peroxide reagent), which keeps for three months. Wash a white porcelain "spot-test" tile with cavities, rinse with 95% spirit, and allow to dry. Do not dry with a cloth, for fragments of fibre may give false positives. Place a "small knife-point"—about 3 mg. or the volume of a grain of rice—of *o*-tolidine hydrochloride in a cavity; add one drop of urine. Stir with a clean glass rod and add one drop of "acid peroxide." A positive reaction appears as a blue coloration, or spreading blue-green streaks which fade after 5–30 minutes to brown. A negative reaction is pale brown.

Results

The results are shown in the Table. Column A gives the number of cells per ml. which can be detected by the techniques described; column B the corresponding concentration of haemoglobin in mg. per 100 ml. of urine;

Method	A	B	C	D
Microscopical*	5×10^3	0·015	100	Nil
o-Tolidine	5×10^4	0·15	10	Nil
Benzidine	5×10^5	1·5	1	4
Kastle–Meyer	5×10^5	1·5	1	Nil
Amidopyrine	10^6	3·0	0·5	2·5
Guaiac	$2·5\times10^6$	7·0	0·2	5
Spectroscopy*	$2·5\times10^6$	7·0	0·2	Nil

* The sensitivity of both these methods can be increased at least fivefold, as described above under "Technique."

column C the relative sensitivities as percentages of that of the centrifuged deposit; and column D the inhibition caused by ascorbic acid (lowest positive concentration without ascorbic acid divided by lowest positive concentration with ascorbic acid).

Technical Difficulties

In the presence of pus all these tests give false positives, which are prevented by boiling the urine; but this treatment reduces sensitivity at least tenfold. All except the Kastle–Meyer give false positives with iodides, and the *o*-tolidine with bromides.

Guaiac.—The tincture of guaiacum resin must be made up weekly, for its sensitivity diminishes on keeping. Some workers prepare an approximately 2% alcoholic solution of the resin at the time of testing. The tubes used are difficult to clean, and if not quite clean give false positives.

Amidopyrine.—The reagent is stable. Tubes are easy to clean and few false positives develop.

Kastle–Meyer, or Reduced Phenolphthalein.—The reagent is troublesome to prepare, but can be bought from B.D.H. at a cost of less than 1d. a test. It deteriorates little on keeping if a little zinc dust is added, but such solutions may require filtration through a hardened filter paper (Whatman 5, 50, or 54) before use. False positives are few. Ascorbic acid does not reduce the sensitivity.

Benzidine.—The reagent must be made up at the time of use from benzidine, glacial acetic acid, and hydrogen peroxide. False positives occur even when tubes appear to be clean. Ascorbic acid reduces the sensitivity about four times.

Orthotolidine Hydrochloride.—The reagents are stable for at least three months. The test is the most sensitive of all and gives few false positives. Ascorbic acid in the concentration used did not reduce the sensitivity.

Conclusion

No single test can be ideal under all conditions. Microscopy of the centrifugal deposit is at least 500 times more sensitive than the guaiac test, and if the Addis procedure be used the ratio reaches 2,500.

For domiciliary work, and as a ward test, the *o*-tolidine hydrochloride test is convenient, very sensitive, and cheap. The porcelain plate can be replaced by a cavity slide 3 by 1 in. (7.5 by 2.5 cm.) to make it more portable. Although in our hands it is much less sensitive for detecting red cells than was claimed by Zwarenstein, it is still ten times more sensitive than any other chemical test, and rarely gives false positives.

The other tests are much less sensitive. The Kastle–Meyer test is very reliable, but the caustic nature of the reagent makes it unsuitable for domiciliary practice. The guaiac test is expensive, insensitive, and not very reliable; it should be abandoned. Should a test of comparable sensitivity be needed, the amidopyrine test is suitable.

In the laboratory it is preferable to examine a centrifuged deposit. If information on the degree and persistence of haematuria alone is needed, then it is justifiable to examine a 1 in. (2.5 cm.) layer of urine with the hand spectroscope; if positive, haemoglobin equivalent to about 2,500,000 red cells per ml. is present; and if negative, then the deposit from 12.5 ml. of urine should be suspended in 0.5 ml. and examined in a Fuchs–Rosenthal chamber.

REFERENCES

Barach, J. H., and Pennock, L. L. (1943). *J. Amer. med. Ass.*, **114**, 640.

Harrison, G. A. (1947). *Chemical Methods in Clinical Medicine*, 3rd ed. Churchill, London.

Kohn, R., and Watrous, R. M. (1938). *J. biol. Chem.*, **124**, 163.

Zwarenstein, H. (1949). *J. clin. Path.*, **2**, 145.

GLANDULAR FEVER WITH NEUROLOGICAL COMPLICATIONS

BY

J. S. CROWTHER, M.D., M.R.C.P.

Senior Medical Registrar, Chase Farm Hospital, Enfield, Middlesex

Epstein and Dameshek (1931) are usually credited with the first description of involvement of the central nervous system in glandular fever (infectious mononucleosis), though Longcope (1922) and Glanzmann (1930) had suspected the association.

I have been able to find only 24 cases of glandular fever, confirmed by a positive Paul–Bunnell test and involving the nervous system, in the literature since 1931 (Sucher and Schwarz, 1936; Gsell, 1937; Pietzonka, 1939; Thomsen and Vimtrup, 1939; Marshall, 1939; Thelander and Shaw, 1941; Landes *et al.*, 1941; Richardson, 1942; Zohman and Silverman, 1942; Hiller and Fox, 1943; Coogan *et al.*, 1945; Ricker *et al.*, 1947; Field, 1948; Bercel, 1948). However, several cases of neurological involvement in clinical glandular fever with a suggestive blood picture but without a positive Paul–Bunnell test have been reported, the most recent being that by Kløvstad (1950); and several cases of proved glandular fever without clinical involvement of

the nervous system have been found to have abnormal cerebrospinal fluids, notably those of Schmidt and Nyfeldt (1938) and Huber (1938). Of the above 24 cases only four had pure encephalitis, the others showing encephalomeningitis, meningitis, cranial nerve lesions, or peripheral nerve lesions. Several of the cases had a radiculo-neuritis of the Guillain–Barré type with raised protein but normal cells in the C.S.F.

The following case of encephalitis in glandular fever is presented because of its rarity.

Case Report

A draughtsman aged 20 had a mild sore throat with pyrexia to 99.6° F. (37.6° C.) for two days and then returned to work although feeling weak. Two days later he had nausea, and next day vomited undigested food. Anorexia, nausea, and occasional slight vomiting of food and bile continued daily until admission to hospital 12 days after the onset. The day before admission he complained of dizziness on sitting up, but not of double vision, and at no time was there pain or headache; he was afebrile after the first two days. There was nothing relevant in either his past or his family history.

On admission to hospital he was afebrile, alert, and co-operative, though preferring to lie on his back with only one pillow, as movement caused dizziness, nausea, and sometimes vomiting. The pulse rate was 76. The only abnormal physical signs were slight injection of the fauces, pea-like glands bilaterally in his neck and axillae, and a doubtfully palpable spleen. Although glandular fever was strongly suspected on clinical grounds, and a blood count and Paul–Bunnell test were requested, a lumbar puncture was also performed. The C.S.F. showed: pressure, 80 mm.; clear; no block; protein, 15 mg. per 100 ml; Pandy, negative; cells, *nil*; W.R., negative.

Other tests were:—Blood count: white cells, 5,300 (polymorphs 45%, eosinophils 6%, lymphocytes 46%). Sedimentation rate, 7 mm. in one hour. Paul–Bunnell test, positive to 1 in 12,800 after guinea-pig kidney absorption and 1 in 3,200 after ox cell absorption. Blood W.R. negative. Liver-function tests: Van den Bergh direct, delayed positive; indirect, 0.7 mg.; thymol turbidity, 6; alkaline phosphatase, 8; cephalin-flocculation test, +++. Plasma proteins: albumin, 4.8%; globulin, 2.5%.

Progress

The spleen became easily palpable two days after admission. Anorexia, nausea, and sporadic vomiting continued for a further 10 days in spite of varied symptomatic treatment, while dizziness was provoked on the slightest attempt to sit up. Sixteen days after admission, and 30 days after the onset of the sore throat, he was noticed to be drowsy and confused, his speech was slurred, and on questioning he complained of severe frontal headache and double vision since the previous day. He also had some difficulty in initiating micturition. He was apathetic and still afebrile. The glands and spleen were still palpable. There was a suggestion of bilateral ptosis; the pupils reacted to light and accommodation but hippus was present, and the fundi were within normal limits. Ocular movements showed limitation laterally, left more than right, with nystagmoid jerks, and gross limitation of upward movement with definite nystagmus. There was diplopia on looking laterally. Other cranial nerves were normal. Neck rigidity was not present. The arms were normal. Abdominal reflexes were absent. Knee- and ankle-jerks were very brisk but equal; ankle clonus was present, but Kernig's sign was negative. There was no response to plantar stimulation.

A diagnosis of glandular fever with encephalitis seemed justified. The following investigations were done:—C.S.F.: clear; pressure, 80 mm.; protein, 15 mg. per 100 ml.; Pandy, negative; cells, less than 1; chlorides, 730 mg. per 100 ml.; glucose, 61 mg. per 100 ml. Paul–Bunnell test with C.S.F. negative. Lange curve, no change. The W.B.C. numbered 5,800, with 55% lymphocytes, many atypical.

The following day his condition appeared worse, he was stuporous, and in his confusion during the night he attempted to get out of bed and fell, but without sustaining any injury. Chloramphenicol was begun because of favourable reports by Hirsch (1949) and by Lewis (1949) on its use in uncomplicated cases. He was given 3 g. daily in four divided doses for two days, followed by 2 g. daily for a further eight days, a total of 22 g. After two days the patient was definitely less drowsy, and able to take a light diet. The physical findings were unchanged, except that the plantar responses were possibly extensor.

A week later he had some dizziness and frontal discomfort on moving his head or eyes quickly, his diplopia was slight and only on looking to the extreme right. The ocular movements were full, and without nystagmus. His speech was normal, abdominal reflexes were present, lower limb reflexes were still brisk, but ankle clonus had vanished. Plantar reflexes were not obtained. The cervical glands were subsiding; the spleen was impalpable. Ten days after this his only complaint was of easy fatigue and lack of concentration—for example, when playing cards or reading. Physical examination was negative, the plantar reflexes both being flexor and the C.S.F. normal. He was discharged for convalescence after 11 weeks in hospital. During this time repeated blood counts never showed haemoglobin below 100% or W.B.C. more than 6,500 per c.mm., with a persistent lymphocytosis of 46 to 65% and even 53% on the day of discharge. Liver-function tests a week before discharge still showed thymol turbidity 4, but plasma globulin had diminished to 1.9 g.% and the cephalin-flocculation test was now only doubtfully positive.

He was seen as an out-patient two months after discharge. Apart from tiring easily, he had no symptoms or signs. W.B.C. numbered 6,400 per c.mm., 52% lymphocytes (none reported as abnormal). The Paul–Bunnell test was still positive; unabsorbed serum was 1 in 40, after guinea-pig kidney absorption 1 in 320; after ox-cell absorption there was no agglutination.

Discussion

This case appears unusual in several respects. At no time after admission to hospital was the patient febrile. It is well known that glandular fever can show afebrile periods, but in the cases reported with nervous complications a raised temperature was present at some time.

Another surprising feature, considering how severely ill the patient was and with such marked neurological signs, was the continued normality of the C.S.F., which was tested once before the onset of definite clinical neurological involvement three times during and once after all neurological signs and symptoms had subsided. Bercel (1948) states that some cases may be missed if the symptoms are slight, as the C.S.F. changes occur late, and this may account for several cases being reported with normal fluid. Among the other reported cases all combinations of raised cells and/or protein were found.

I have been able to trace only four fatal cases (Thomsen and Vimtrup, 1939; Ricker *et al.*, 1947), all the others having made complete recoveries without any specific treatment; and indeed Tidy (1948) has pointed out that improvement in neurological cases begins within a few days of the patient's lowest ebb. Nevertheless, this patient appeared so desperately ill at one stage that it was decided to use chloramphenicol. Of the two reported cases treated with chloramphenicol, one, that of a child who responded clinically within 24 hours of beginning the drug, was given the drug for three days.

only, but she relapsed a week later. She again responded promptly when again given the drug, and this was continued for one week without further relapse. The other case, of seven months' duration, responded promptly, and had not relapsed three months after discontinuance of the drug. Although most cases of glandular fever are relatively benign and require only symptomatic treatment, some severe ones often leave behind a state of depression and debility which may predispose to more serious illness (indeed, I have seen two cases which within a few weeks returned with a tuberculous pleural effusion), and in these cases if chloramphenicol is likely to shorten the illness it may be worth a trial.

Summary

A case of glandular fever with encephalitis is reported. The Paul–Bunnell test was positive, and the blood showed typical cell changes.

In spite of the clinical encephalitis, the cerebrospinal fluid was normal on the five occasions it was tested.

Chloramphenicol was used in treatment: its use in glandular fever is discussed.

I wish to thank Dr. C. Allan Birch, into whose ward this patient was admitted, for his interest and help in the preparation of this article.

REFERENCES

Bercel, N. A. (1948). *J. nerv. ment. Dis.*, **107**, 537.
Coogan, T. J., Martinson, D. L., and Mathews, W. H. (1945). *Illinois med. J.*, **87**, 296.
Epstein, S. H., and Dameshek, W. (1931). *New Engl. med. J.*, **205**, 1238.
Field, W. W. (1948). *Amer. J. Med.*, **4**, 154.
Glanzmann, E. (1930). *Das lymphaemoide Drüsenfieber*. Karger, Berlin.
Gsell, O. (1937). *Dtsch. med. Wschr.*, **63**, 1759.
Hiller, R. I., and Fox, M. J. (1943). *Marquette med. Rev.*, **7**, 152.
Hirsch, F. G. (1949). *Nav. med. Bull., Wash.*, **49**, 1081.
Huber, W. (1938). *Schweiz. med. Wschr.*, **68**, 892.
Kløvstad, O. (1950). *Acta med. scand.*, **139**, 67.
Landes, R., Reich, J. P., and Perlow, S. (1941). *J. Amer. med. Ass.*, **116**, 2482.
Lewis, P. L. (1949). *J. Pediat.*, **35**, 630.
Longcope, W. T. (1922). *Amer. J. med. Sci.*, **164**, 781.
Marshall, E. A. (1939). *Amer. J. clin. Path.*, **9**, 298.
Pietzonka, H. (1939). *Dtsch. Arch. klin. Med.*, **185**, 153.
Richardson, J. S. (1942). *Lancet*, **1**, 618.
Ricker, W., Blumberg, A., Peters, C H., and Widerman, A. (1947). *Blood*, **2**, 217.
Schmidt, V., and Nyfeldt, A. (1938). *Acta oto-laryng.*, **26**, 680.
Sucher, A., and Schwarz, E. (1936). *Wien. klin. Wschr.*, **49**, 1417.
Thelander, H. E., and Shaw, E. B. (1941). *Amer. J. Dis. Child.*, **61**, 1131.
Thomsen, S., and Vimtrup, B. (1939). *Nord. Med.*, **4**, 3295.
Tidy, Sir H. (1948). *Blood*, **3**, 823.
Zohman, B. L., and Silverman, E. G. (1942). *Ann. intern. Med.*, **16**, 1233.

Korea is a highly malarious country with much of the population infected with the disease. In addition, the work of combating the anopheles mosquito has been complicated both by the innumerable breeding grounds provided in rice paddies and by the frequently harassing tactical situation. However, with the use of chloroquine, which became available throughout the entire combat area late in the summer of 1950, the incidence of malaria in Korea has been kept low compared with the second world war rates. Chloroquine is an excellent suppressant; but, like mepacrine and quinine, it is neither a preventive nor a complete cure for malaria. It was developed by the Germans in 1939 as a relative of pamaquin. Recently the U.S. Army Medical Service has concentrated much of its research on a new drug, primaquine, which appears particularly effective against the tissue phase of the disease because it attacks the stubborn parasites in the liver cells. This is chemically another close relative of pamaquin, merely differing in having a primary amine instead of a tertiary amine at the end of its side chain. A preliminary report appeared in the *Journal of the National Malaria Society*, 1950, **9**, 285.

TENOSYNOVITIS OF THE WRIST

BY

MAURICE ELLIS, F.R.C.S.

(From the General Infirmary, Leeds)

Gray's Anatomy (1949) describes this disease in the following words: "The tendons of the abductor pollicis longus and the extensors of the thumb are liable to become strained and their sheaths inflamed (tenosynovitis) after excessive exercise, producing a sausage-shaped swelling along the course of the tendons." In three standard textbooks of surgery, tenosynovitis is described similarly as a disease of these three muscles of the thumb. One of them amplifies this description by stating that it is a disease of the "tendon sheath of the extensor ossis metacarpi pollicis (abductor pollicis longus) and of the extensores longus and brevis pollicis . . . and as the sheath surrounds not only the tendons but, as can be anatomically demonstrated, also extends some way up around the muscle bellies, movements of the affected parts are painful" (Romanis and Mitchiner, 1948).

Examination of 44 cases since the beginning of 1949 has made me very dissatisfied with this anatomical description. The disease as met with in the casualty department of the General Infirmary, Leeds, presented the following anatomical features. A sausage-shaped swelling was present on the radial side of the lower part of the dorsal surface of the forearm. This swelling was always about 1½ in. (3.8 cm.) long, and appeared to be slightly oblique to the long axis of the forearm. The lower limit of this swelling never extended distally beyond a point about 2 in. (5 cm.) from the lower articular margin of the radius. Thus, even allowing for a tendon sheath extending around the muscle bellies as described by Romanis and Mitchiner, the swelling seemed to be too high in the forearm to have any connexion with the extensors and long abductor of the thumb.

To investigate this point, therefore, a number of dissections were made on the lower forearm in the post-mortem room. My dissections all showed conclusively that the muscle bellies and tendons of the three dorsal muscles of the thumb crossed obliquely over the radius in its lower 2 in., and thus were unlikely to have any connexion with the swelling of tenosynovitis as seen clinically. Injections of water into the sheaths surrounding the tendons of these muscles did confirm the description given by Romanis and Mitchiner of the tendon sheath continuing up over the bellies of the muscles of the thumb, but the swelling produced by this distension of the sheath did not in the least resemble the shape of the swelling seen clinically, and was situated too near the wrist to correspond with the site of the swelling seen clinically. Dissections further up the forearm show that, immediately proximal to the muscles of the thumb, the tendons of the extensores carpi radialis longus and brevis are lying subcutaneously and that these tendons pass deep to the muscles of the thumb as they proceed distally to their insertion. These tendons emerge from their appropriate muscle bellies at a point about 1½ in. proximal to the upper border of the muscles of the thumb. Injections of water into the areolar tissue surrounding these tendons always produced a sausage-shaped swelling exactly similar to that seen clinically in tenosynovitis. The apparent obliquity of the swelling is shown to be produced by the oblique passage of the muscles of the thumb over the tendons. If the muscles of the thumb

are divided and retracted before the injection is made, the distension is seen to proceed downwards towards the wrist, but it is very much restricted in size. Dissection into the swelling showed a glairy shining lining typical of synovial membrane. The proximal limit of this synovial sheath is very sharply demarcated at the point of origin of the tendons from the muscles. The distal limit of the sheath is much more indefinite, but when the muscles of the thumb are in place it appears to be sharply demarcated.

It is thus clear that the description of tenosynovitis as a lesion of the muscles of the thumb is inaccurate. It is, in fact, a lesion of the sheath of the tendons of the extensores carpi radialis.

Cause

The disease is said to be due to a strain or excessive use of muscles. In the 44 cases which form the basis of this paper the causes of onset can be divided into main groups.

1. Direct trauma, in which there is a history of a blow directly on to the tendon sheath as it lies subcutaneously (13 cases).

2. Indirect trauma, in which the lesion follows use of the tendons. These can again be subdivided into three: (*a*) those following one isolated excessive muscular action (9 cases); (*b*) those following a series of unaccustomed movements of the wrist (19 cases), the most common type; (*c*) those in which no definite cause could be ascertained (3 cases), although in two of them a recent illness was a probable factor.

From an inquiry into movements preceding the cases of indirect trauma, it is postulated that the lesion occurs under the following conditions. The hand is firmly grasping some object, thus fixing thumb and rendering the three dorsal muscles of the thumb tense and hard; the tendons of the extensores carpi radialis are now lying in a rigid tunnel. A sudden fierce movement of hyperextension or a series of hyperextension movements of the wrist—such as might be done by a person performing unaccustomed wrist movements or with the muscles not adequately toned up, as after an illness—lifts up the tendons of the extensores carpi radialis like a bowstring away from the radius and against the taut thumb muscles, as the bases of the metacarpals, where these tendons are inserted, move dorsally. This trauma produces the tenosynovitis. Once the lesion is present, movements of the thumb muscles over the continuation of the sheath deep to these muscles, which I demonstrated in my dissections, will produce pain. It is possibly for this reason that attention was directed to the thumb muscles as being primarily involved and the inflammation was inaccurately located in their tendon sheaths. This inaccuracy would appear to have been copied from textbook to textbook.

Clinical Picture

The patient usually comes complaining of pain at the back of the wrist or lower forearm. With this there is sometimes weakness of the grip. On examination the sausage-shaped swelling previously described is discovered. This swelling may be hot and tender to the touch; this is usually so in the cases which follow sudden direct or indirect trauma, whereas in the other cases these signs are not so common. Crepitus over this swelling was always found to be present on movements of the wrist. The amount of crepitus varied from case to case, but I could not discover that it bore any relation to the degree of swelling. This crepitus can be palpated over the swelling, beneath the bellies of the muscles of the thumb, and in some cases at the bases of the metacarpals, where the extensor carpi radialis is inserted. More than one case was sent to me by the general practitioner as a fracture because of the discovery of this well-marked crepitus. More often, however, the presence of crepitus was not discovered. As the lower part of the coat-sleeve covers the site of the swelling and crepitus, it is presumed that the sleeve had not been drawn back when the practitioner's examination was made. As previously pointed out, owing to the extension downwards of the inflamed sheath beneath the muscles of the thumb, the pain may subjectively be centred on movements of the thumb, and thus the examiner may easily be misled and omit the examination higher up the forearm.

Treatment

Many forms have been described, and these can be divided into three groups; (*a*) rest; (*b*) electrotherapy of all kinds; (*c*) counter-irritants.

Rest.—This is usually carried out by splintage with plaster-of-Paris or by other means. There is no doubt that immobilization of the hand and wrist in plaster-of-Paris rapidly brings about relief of the pain. Unfortunately, it has been my experience that as soon as the plaster is removed and the hand is used again, the pain recurs. Rest in a sling has been recommended, but this compromise does not give such an efficient relief of pain. Another form of treatment which might come under the category of rest is the wearing of a strapping round the wrist. The leather wristband beloved and almost the hallmark of the old-type "navvy" is of the same nature. In view of the anatomy of the condition it is difficult at first sight to understand why such an appliance should give the relief that its wearers claim. It is suggested that the wristlet does not work by mere pressure over the muscles of the thumb and the extensor sheath, but, because the lower edge of the leather strap impinges on the back of the hand, it prevents hyperextension of the hand and thus the bowstring position of the extensores carpi radialis which is the cause of the lesion.

Electrotherapy.—Radiant heat, infra-red rays, and short-wave diathermy have all been tried with varying success, and no specific has been found among them.

Counter-irritants that I have used have been ung. iodi (*B.P.*) or its equivalent, and occasionally Scott's dressing.

In assessing the value and results of treatment, however, it must be borne in mind that the majority of sufferers from this complaint earn their living by their hands. Other things being equal, a form of treatment which keeps the patient away from work, such as immobilization in plaster, is undesirable. Similarly, electrotherapy, which necessitates the patient breaking work for visits to the hospital, is to be avoided if possible. Therefore simple counter-irritants which can be applied by the patient himself and do not of themselves cause stoppage of work have everything to recommend them.

The following is the routine of treatment now evolved in our casualty department. In the first place, it is explained to the patient that to stop work and immobilize the wrist in plaster-of-Paris will give a speedy relief from pain, but when the plaster is removed and the wrist is used again there is no guarantee that the pain will not recur. The patient is exhorted to continue at work and to rub ung. iodi into the swelling twice daily. The patient is assured that the pain will then slowly disappear and will not recur.

It has been found that by this means the majority of cases clear up in one to three weeks. One case, which had been treated in plaster at a hospital remote from Leeds and had a recurrence of pain when the plaster was removed after six weeks, recovered completely in two weeks by this treatment. In three cases the pain was so intense that the patient had to give up his manual work for two weeks, and recovery occurred in about six weeks. In cases in which the pain persisted although this regime was carried out, electrotherapy was added, but the patient continued at work.

Summary

Clinical observations and dissections have shown that the current description of the anatomical background of tenosynovitis of the wrist is inaccurate. It is not, in fact, a lesion of the tendons of the long muscles of the thumb, but a lesion of the tendon sheaths of extensores carpi radialis.

The mode of onset of 44 cases as seen in Leeds is described and classified. A rational anatomical background, in view of the new knowledge, is propounded for all these cases.

The clinical picture of the lesion is described.

Various methods of treatment are discussed. The routine treatment, by means of ung. iodi, as carried out in Leeds General Infirmary, cleared up most of the cases in one to three weeks.

REFERENCES

Gray's Anatomy (1949). 30th ed., p. 623. Longmans, London.
Romanis, W. H. C., and Mitchiner, P. H. (1948). *Surgery*, 8th ed., 1, 403. Churchill, London.

Medical Memorandum

Intestinal Actinomycosis Treated with Chloramphenicol and Aureomycin

Case Report

Two months after an operation for a perforated appendix a man aged 35 was readmitted to hospital with a tender mass in the right iliac fossa. Penicillin, 250,000 units intramuscularly, was given six-hourly for seven days.

At laparotomy on June 15, 1949, a sausage-shaped process of induration was seen extending along the ascending colon. Pus was not found. During the next two months abscesses were incised in the right iliac and lumbar regions. A combined course of penicillin (100,000 units intramuscularly three-hourly for 10 days) and sulphadiazine (36 g.) was given without effect. During the next four months the sinuses were twice explored and two courses of streptomycin (19 g. and 42 g.) were given. No treatment had so far affected the pyrexia, which had been present throughout, or caused any healing of the sinuses.

On February 22, 1950, following incision of an abscess, actinomycetes were found in the pus. Penicillin was then administered in larger dosage (1,000,000 units thrice daily for eight weeks), but at the end of five weeks the general condition was, if anything, worse. Investigations at this stage showed: 2,800,000 red cells per c.mm.; Hb, 48%; white cells, 23,000 per c.mm. (polymorphs 87.5%); E.S.R. (corrected Wintrobe), 31 mm. in first hour; serum albumin, 2.2 mg., and serum globulin, 3.6 mg. per 100 ml.; alkaline phosphatase, 12 units; thymol turbidity, 9 units; thymol flocculation, +++; weight, 101 lb. (45.8 kg.).

As penicillin did not seem to be affecting the course of the disease, chloramphenicol was begun on March 31, the dosage being 0.5 g. four-hourly for two days, 0.5 g. eight-hourly for three days, 0.25 g. eight-hourly for 12 days, and 0.5 g. eight-hourly thereafter. Within a week the patient

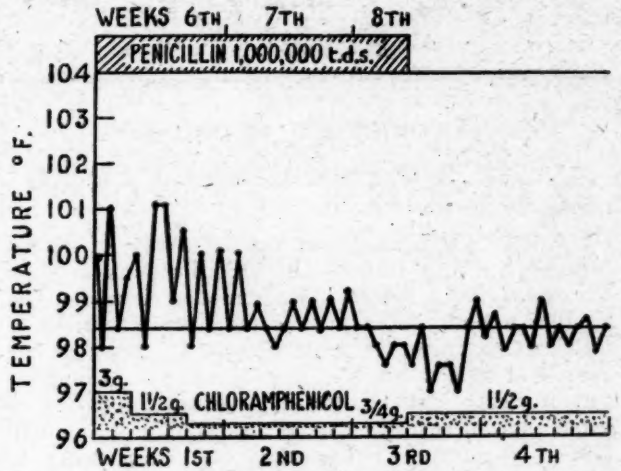


FIG. 1.—Temperature chart during chloramphenicol treatment.

reported that he felt very much better, and by the end of the second week his temperature was normal (Fig. 1). Improvement was maintained for about four weeks, during which he gained 5 lb. (2.3 kg.) in weight and the sinuses were healed.

After six weeks pyrexia recurred, and on June 2 an abscess was incised in the right iliac fossa. Actinomycetes were again demonstrated in the pus. Treatment was continued for a further week, but the temperature failed to settle and the general condition deteriorated.

"Aureomycin" was started on June 15, the dosage being 0.5 g. four-hourly for 24 hours, 0.5 g. six-hourly for five days, 0.5 g. eight-hourly for 37 days, and 0.25 g. eight-hourly for 64 days. Clinical improvement, which was quite dramatic, was apparent within the first few days (Fig. 2).

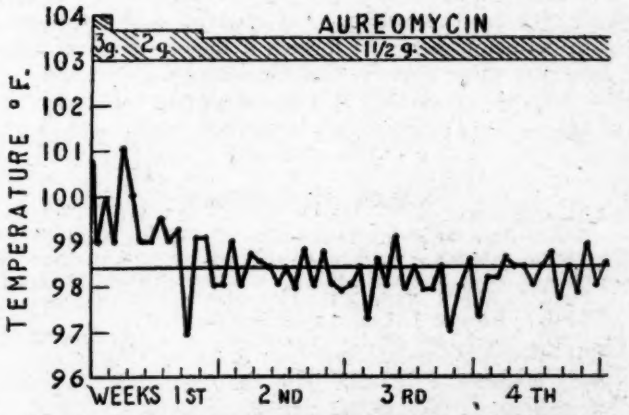


FIG. 2.—Temperature chart during aureomycin treatment.

The temperature began to settle at the end of a week and, apart from an occasional evening rise to 99° F. (37.2° C.), remained normal. He gained weight rapidly—16 lb. (7.3 kg.) in the first month. E.S.R. estimations showed progressive decrease.

Aureomycin was discontinued on September 29, when investigations were as follows: 4,700,000 red cells per c.mm.; Hb, 93%; white cells, 8,000 per c.mm. (polymorphs 76%); E.S.R. (corrected Wintrobe), 12 mm. in first hour; serum albumin, 4.7 mg.; serum globulin, 3.9 mg.; alkaline phosphatase, 6 units; thymol turbidity, 6 units; thymol flocculation, 0.

Improvement has been consolidated, and 12 months after the beginning of aureomycin treatment the patient has been working for four months, wounds and sinuses have remained healed, he feels perfectly well, and weighs 150 lb. (68 kg.).

H. H. D. KELLY, M.B., B.Ch., B.A.O.

Reviews

TEXTBOOK OF MEDICINE

A Textbook of Medicine, edited by E. Noble Chamberlain, M.D., M.Sc., F.R.C.P. (Pp. 962. 50s.) Bristol: John Wright and Sons, Ltd. 1951.

Dr. Noble Chamberlain has collected a team of sixteen colleagues, mostly from the Liverpool region, to write a textbook which stresses the commoner diseases. The result is a book about a third the size and weight of the latest American textbooks on internal medicine, but even so it runs to nearly a thousand pages. Compression is clearly difficult, for it is almost impossible to avoid allotting space to diseases according to the amount known about them rather than their importance in theory and practice. Thus, little more than a page is given to all forms of acute and subacute hepatitis, while four pages are given to tetany; on a larger scale there is the contrast between 67 pages on digestive diseases and 135 pages on organic nervous diseases.

Nevertheless, one can welcome this book as likely to prove useful and popular with students. It comes from a good stable and is produced in the same format as Chamberlain's deservedly popular *Symptoms and Signs in Clinical Medicine*. The text is well printed and diversified with illustrations in a way likely to appeal to the student, though it is doubtful if the colour photographs justify themselves. It is invidious to single out authors for special mention, but the sections on diseases of the nervous system by Nattrass and on tropical diseases by Maegraith and Adams are particularly good, as are the illustrations to diseases of the digestive system. One may question whether it is desirable to put patients with pernicious anaemia to bed, if they have not found their way there already, and the misprint of "insulin" for "inulin" on p. 459 is likely to puzzle the student.

L. J. WITTS.

X-RAY DIAGNOSIS

A Textbook of X-ray Diagnosis. By British Authors. Second edition. Volume I. Edited by S. Cochrane Shanks, M.D., F.R.C.P., F.F.R., and Peter Kerley, M.D., F.R.C.P., F.F.R., D.M.R.E. (Pp. 434; 439 illustrations. £2 5s.) London: H. K. Lewis and Co. 1951.

This volume is the last to appear in the new edition of a great textbook. It deals with the most difficult fields of radiology—the central nervous system and skull—and the high standard of the book is a tribute to the ability and experience of its authors. To the technical difficulty of *x*-raying the skull is added the complexity of the conditions which occur, and both these are discussed with remarkable skill.

A detailed discussion on general technique and the anatomy and pathology of the skull is followed by a chapter on radiological features of the cranium, normal and abnormal. Both are profusely illustrated with photographs, radiographs, and diagrams which bring out many points of interest. The sections on the sella turcica and the base of the skull are of special value. A long chapter is devoted to ventriculography and encephalography, and the technical details of these important methods are fully described. The illustrations and discussion draw on a great wealth of material and give a clear view of the possibilities and limitations of the methods. The account of angiography is constructed with equal care and is a high achievement of team work. The practical use of these methods is revealed in a brief but clear general account of intracranial lesions, including cerebral tumours, haemorrhage, abscess, and hydrocephalus. The chapter on the spinal cord might have been further extended. Carcinoma of the spine and prolapse of intervertebral disks are not illustrated, in spite of their neurological importance. Myelography for spinal tumours is well discussed.

To the mere surgeon the article on the teeth and jaws is a revelation of what can be achieved in this region by radiography. The illustrations are very fine and show the complete revolution which the *x* ray has effected in dental surgery and the splendid use which dentists have made of their new weapon. In the eye radiography has a limited field, but even here the methods devised for the location of foreign bodies provide examples of superb technique. Radiography of the accessory nasal sinuses and the temporal bone is a field whose difficulty equals its importance. The anatomy, physiology, and pathology are all admirably described and beautifully illustrated.

The whole volume is a magnificent achievement of team work of which the authors may well be proud. It completes a textbook which puts British *x*-ray diagnosis in the leadership of the world.

HENRY SOUTTAR.

A HISTORY OF MEDICINE

Geschichte der Medizin im Überblick. By Th. Meyer-Steineg and Karl Sudhoff. Fourth edition. Edited by Benno von Hagen. (Pp. 460; 224 illustrations. M. 18.) Jena: Gustav Fischer. 1950.

This is the fourth edition of the history of medicine by Th. Meyer-Steineg and Karl Sudhoff, first published in 1921. The text has not been greatly enlarged, but many little alterations or corrections have been made since the first edition. For instance, the exact reference to the quotation from Spinoza on p. 142 has been added, which shows the care taken in the accuracy even of such details. The wealth of illustrations is a feature of the book. They help to explain the text, and certainly attract the attention of many readers.

Few can remember Professor Sudhoff when he was a guest of honour at the dinner given by Sir Norman Moore, as President of the Section of Medical History at the International Medical Congress held in 1913 in London. At that time Sudhoff had already mapped out work enough to occupy the rest of his life. His chief work on Paracelsus was to be left till near the end, and in fact his edition of Paracelsus's works did not appear till 1933. Sudhoff died in 1938. In the present book Paracelsus and his place in medicine are considered at some length (pp. 270–278).

For those who read German the present edition holds its own as a useful and interesting reference handbook on the long history of medicine. It takes us from the beginnings in prehistoric times through the periods of Greek philosophy, observation, rational deduction, and relative freedom from superstition, culminating in the Hippocratic teaching; then to the "Arabians" with their translations and commentaries, and to mediaeval Europe and the rise of the great European medical schools, culminating in the medical Renaissance and the revolutionary work of Vesalius, Harvey, and all the others leading to the threshold of the brilliant scientific therapeutic discoveries of the present time.

After studying this and other books on the history of medicine we may, like the authors, conclude in Goethe's words (as quoted by F. von Müller): "There is no past, which one should wish to have back again. There is only the eternal new, which is built up from enlarged elements of the past. The new longing must always be productive—to create a better new."

F. PARKES WEBER.

YOUNG DELINQUENTS

Wayward Youth. By August Aichhorn. Foreword by Sigmund Freud. Preface by K. R. Eissler, M.D. (Pp. 236. 9s.) London: Imago Publishing Company. 1951.

The study of delinquency, from both therapeutic and preventive aspects, is rapidly gathering impetus in this and other countries, and through the activities of various United Nations organizations it is about to be brought into international focus. It is hampered in the main by four circumstances: the persistence of ancient moral prejudices enshrined in criminal and penal codes; the fact that a number of disciplines, not all of equal scientific force, are involved in the investigation of the subject; the lack of sufficient trained workers; and the absence of precise aetiological information. This last factor in particular makes the publication of a second and very reasonably priced English edition of the late Dr. Aichhorn's classic work a timely event.

Aichhorn was not, as is often supposed, a psychoanalyst who made a hobby of studies in delinquency. He was in fact an educationist who, looking for scientific guidance in the treatment of antisocial youth, turned from academic psychology to psycho-analysis. The results of his early experiments in applying psychoanalytic principles to the re-education of delinquents were originally published in 1925 in the first edition of *Wayward Youth.* They comprise a somewhat limited, but at that time essential, psychiatric classification of delinquent disorders, an account of the main endopsychic factors responsible for antisocial conduct, and an outline of the principles and practice of the therapy of delinquents, in which last he emphasized the cardinal factor of "transference."

Although much of all this is now taken for granted by workers in the field, Aichhorn's book is still a mine of information, not to say a source of great encouragement, to those who approach this difficult specialty, whether they be psychiatrists, pedagogues, or sociologists. The story of his experiences in handling young, violent psychopaths is in its way an epic and should be taken to heart by those who are accustomed to regard psychopathic states with a jaundiced prognostic eye. On all counts, therefore, this is an indispensable book for all who struggle to teach "problem children," for all servants of the law, and for the forensic psychiatrist.

EDWARD GLOVER.

BACTERIAL CHEMISTRY

The Chemical Activities of Bacteria. By Ernest F. Gale, B.A., Ph.D., Sc.D. Third edition. (Pp. 213. 9s. 6d.) London: University Tutorial Press. 1951.

The author has attempted to produce an account of the chemical activities of bacteria which will be useful to students reading biochemistry, bacteriology, or chemistry and will provide an introduction to more advanced study. He has succeeded in doing so in a book which is both compact and clear. It includes a section on the mode of action of enzymes, the changes that may result from mutation, the distinction between adaptive and constitutive enzymes, and the effects of physicochemical conditions. The section on growth and synthesis of bacterial protoplasm shows the advance in nutritional requirements from the autotrophic bacteria to organisms that need both amino-acids and growth factors, and the ways in which the more exacting mutants are used to study synthetic processes and measure the concentration of nutrients. In other sections he discusses the provision of energy by fermentation and oxidation, the breakdown of nitrogenous materials, and the nitrogen cycle. There is a short discussion of pathogenicity, the natural defences against bacteria, and chemotherapy.

Some minor criticisms can be made. Nothing is said about nucleic acids. In view of the importance of polysaccharides in relation to specificity, more might have been written about them. There seems little reason for specifying the bone marrow as the site of formation of antitoxins. Nothing is said about the chemistry of the classical exotoxins—diphtheria, tetanus, and botulinus—and no mention is made of endotoxins such as that of *Salm. typhi.* The prominence given to the toxic enzymes might lead to an exaggerated impression of their importance in disease.

The book contains much that should interest students of animal metabolism.

J. R. MARRACK.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received

Caelius Aurelianus on Acute Diseases and on Chronic Diseases. Edited and translated by I. E. Drabkin. (Pp. 1,019. 112s. 6d.) London: Cambridge University Press. 1951.

Surgical Nursing and After-Treatment. By H. C. R. Darling, M.D., M.S., F.R.C.S., F.R.F.P.S., and T. E. Wilson, M.D., M.S., M.Sc., F.R.C.S., F.A.C.S., F.R.A.C.S. 10th ed. (Pp. 630. 16s.) London: J. and A. Churchill. 1951.

Clinical Laboratory Methods. By W. E. Bray, B.A., M.D., 4th ed. (Pp. 614. 52s. 6d.) London: Henry Kimpton. 1951.

Essays in Applied Psycho-Analysis. Vol. II. By Ernest Jones, M.D. (Pp. 383. 21s.) London: The Hogarth Press. 1951.

Demography. By P. R. Cox, F.I.A., F.S.S. (Pp. 326. 20s.) Cambridge: University Press. 1950.

Handbook of Gynaecology. By T. L. S. Baynes, M.D., F.R.C.S., M.R.C.O.G. (Pp. 163. 15s.) London: Sylviro Publications. 1951.

Bronchial Asthma. By R. J. Whiteman, M.B., Ch.M., F.R.A.C.S. (Pp. 184. 15s.) London: H. K. Lewis. 1951.

Exercises Before Childbirth. By K. Vaughan, M.B. (Pp. 48. 6s.) London: Faber and Faber. 1951.

A Guide to the Nomenclature used in Organic Chemistry. By E. H. Tinley, B.Sc., Ph.C. (Pp. 16. 1s.) Leeds: Thomas Waide. 1951.

Prehistoric Man in Health and Sickness. Catalogue of an exhibition held at the Wellcome Historical Medical Museum. (Pp. 56. 2s. 6d.) London: Geoffrey Cumberlege. 1951.

An Experiment in the Control of Tuberculosis Among Negroes. By J. Downes. (Pp. 67. No price.) New York: Milbank Memorial Fund. 1950.

Cystektomie beim Blasenkrebs. By Professor H. Boeminghaus. (Pp. 84. M. 11.50.) Stuttgart: Georg Thieme. 1951.

BRITISH MEDICAL JOURNAL

LONDON

SATURDAY SEPTEMBER 29 1951

THE KING'S HEALTH

The news that the King had to return to London from his holiday at Balmoral for a radiological examination was a disquieting sign that his medical advisers were anxious about the lung condition which was first mentioned in a bulletin issued on June 1. As a result of this and other examinations, including bronchoscopy, the decision was made that the structural changes apparent in the lung could best be dealt with by surgical means, and the King underwent an operation for resection of lung on September 23 at Buckingham Palace. Only a few years ago such an operation on the lung could not have been attempted, and the advances in surgery and anaesthesia that make it possible were largely achieved in this country.

All his subjects will now anxiously await reassuring news about the King's progress. In particular members of the medical profession will wish to associate themselves with the good wishes sent by the B.M.A. to the King's Private Secretary in the following telegram:

> The members of the British Medical Association in the United Kingdom and the British Commonwealth and Empire tender to His Majesty the King, Patron of the Association, with an expression of their loyal duty, their sincere sympathy in his illness, and their earnest wishes for His Majesty's early and full restoration to health.

At times of political uncertainty and international tension the citizens of this country and of the Commonwealth have special reason to be grateful for the unifying influence of the Crown. For many years our King has shouldered his heavy responsibilities with unwavering devotion and courage, not even allowing his illness in 1949 to cause more than the minimum interference with his duties, and it is small wonder that his strength has been overtaxed. All the King's subjects, at home and abroad, will at this time of anxiety join in praying for his speedy recovery and restoration to full vigour and health.

PROBLEMS IN HOSPITAL ADMINISTRATION

When giving evidence before the Select Committee on Estimates the chairman of the South-west Metropolitan Regional Hospital Board remarked, "There is a feeling of frustration through the whole (hospital) Service. That is my definite opinion." On being questioned about this by members of the committee he went on to say that the efficiency of the Service was suffering because people who were capable of doing the work well were disinclined to serve on boards and hospital management committees. In his view the solution was less interference from the Ministry of Health. Admittedly this is an individual opinion, but a scrutiny of the Select Committee's informative report (summarized in the *Supplement* this week) on regional hospital boards and hospital management committees shows that hospital administration in the N.H.S. is suffering because of an uneasy compromise between the powers of the Ministry of Health, the regional hospital boards, and hospital management committees.

Fundamentally this is a problem of relations between central and local government. The difficulty is that the regional boards and hospital management committees are not rate-raising bodies like local authorities, and the central government, providing all the money, naturally expects to keep a firm control over expenditure. But it would be against tradition, the interests of the hospital service, and public opinion further to centralize hospital administration. When planning the Health Service the Government was able to use the existing insurance committees as an administrative basis for the general-practitioner service, and of course the public health work could quite properly remain with the larger local authorities, which had long experience in the organization of maternity, child welfare, and similar services. Administratively the Government would no doubt have found it simplest to place the hospitals under the major local authorities, but there were several insuperable objections to this. For one thing, only a few of the larger local authorities had made a success of the powers given to them under the Local Government Act of 1929, which transferred institutional care of the sick from the old boards of guardians to county and county borough councils. Furthermore, the medical profession was strongly opposed to any proposal that local authorities should be made responsible for the hospital service. Dr. T. Rowland Hill, giving evidence before the Select Committee on behalf of the B.M.A., was most emphatic on this point, though he indicated that there should be more local representation on

hospital management committees and less ministerial selection. As a step in the right direction he suggested that members of regional hospital boards might be elected by the hospital management committees of the region. Moreover, a number of regional boards have no general-practitioner members, though there is no doubt that there should be one on every board. Uneasiness about the method of selection of members of hospital boards and management committees is not confined to the medical profession, though few will question the great value to the country of the voluntary services of those who have undertaken a time-consuming and usually thankless task.

A commonly heard criticism of the new hospital service is that since the appointed day there has been a great increase in administrative staff. In the area of the Sheffield Regional Hospital Board, for instance, 1,017 persons were employed in clerical or administrative jobs on July 5, 1948, at a cost of £319,963 per annum. By March 21, 1951, the numbers had gone up to 1,658 and the cost to £563,653. Such increases are an inevitable outcome of State control: the spending of public money has to be much more meticulously supervised and recorded than the spending of money which in the old days was the private property of the hospital. Hence the need for accountants and clerks to check and double-check. Unfortunately regional hospital boards have inadequate powers to curtail the exuberant expansion of some management committee staffs, and the Select Committee recommends that the boards should be given the responsibility of controlling establishments.

The present inflexibility of the system of itemizing proposed expenditure is particularly unsuitable for hospitals, and the refusal of the Ministry to allow unexpended balances to be carried over leads to overestimating and a scramble to spend all the money allotted under one head within the financial year. Regional boards have little time to examine the estimates of the management committees in their area and are in a weak position to check extravagance. In fact the chairman of one management committee told the Select Committee that, since the regional boards had to go to the Ministry to obtain approval for practically everything, he felt that they could be dispensed with and that hospital management committees could deal direct with the Ministry.

Evidence given before the Select Committee certainly made it plainer than ever that the present method of financing the hospitals is both dilatory and wasteful. The Ministry must soon decide whether the regional boards are to have any control of expenditure in the hospital service or whether they are to have only planning and advisory functions. Without adequate financial powers they cannot take an effective place in the two-tier system of administration of which so much was hoped.

CANCER OF THE TONGUE

Although the incidence of lingual carcinoma has diminished in recent years the disease still causes about 700 deaths a year in this country. Surgical treatment, based on the often extensive operations conceived at the end of the last century, culminated in the work of Butlin,[1] who in 1908 was able to report three-year survivals in 28% of 197 cases treated since 1881. Progress in surgery since then has been mainly in the efficacy of block dissection for the lymph node areas and in the use of electrodiathermy in selected primary tumours. As radium has more and more become the main weapon of attack on the primary disease, so the demands for surgery have been narrowed to a few well-defined indications. According to Sir Stanford Cade,[2] glossectomy is indicated in about 7% of cases, including those in which the disease has spread to the floor of the mouth to involve the mandible; those with a hard infiltrating growth affecting the whole tongue in the anterior part down to the V of circumvallate papillae; and those with recurrence or residue of growth after radium therapy. The Clinical Cancer Research Committee[3] of the British Empire Cancer Campaign has recently analysed 331 cases of cancer of the tongue (287 primary and 44 recurrent). Of patients with growths in the anterior two-thirds 36 were treated by surgery alone, 28 by combined methods, and 122 by radiotherapy alone. Nearly all the patients with growths in the posterior one-third were treated by radiotherapy alone.

Radium has now been used long enough for an appraisal of its value, and particular interest attaches to a series of papers[4] on the end-results of treatment of cancer of the tongue presented to the American Radium Society in 1948 and more recently published as a symposium. Dr. Juliette Baud described a series of 1,055 patients treated at the Fondation Curie in Paris from 1919 to 1941, mainly by interstitial radium. The best results (5-year cure in 21% of patients) were obtained when the growth was on the dorsum or edges of the tongue. The 5-year cure rate was reduced to 15% when the growth was on the tip or undersurface, while only 10% of patients with growths arising in the posterior third survived for

1 *On the Results of Operations for Carcinoma of the Tongue*, 1908, London.
2 *Amer. J. Roentgenol.*, 1950, **63**, 716.
3 *Annual Report for 1950 of the British Empire Cancer Campaign*, 1951, London.
4 *Amer. J. Roentgenol*, 1950, **63**, 701.
5 *Researches on the Radiotherapy of Oral Cancer, Spec. Rep. Ser. med. Res. Coun., Lond.*, 1950, H.M.S.O., London.

five years. The figures for late recurrences (after 6 to 21 years) show the need for caution: these occurred in 4 out of 13 growths on the tip and undersurface, in 31 of 135 growths on the dorsum and edges, and in 8 of 34 growths on the posterior third of the tongue. Dr. Elis Berven, of Radiumhemmet, Stockholm, reported on 267 patients treated between 1931 and 1942 by teleradium and electrocoagulation of the primary tumour, and teleradium and block dissection of the regional nodes. He recorded a relative five-year cure and survival rate of 28.1%, with an addendum that in 1938–44 this had improved to 34%. Sir Stanford Cade favoured interstitial radium in anterior lesions and teleradium in those arising posteriorly. He emphasized the importance of radical block dissection of the neck when certain conditions are satisfied: the primary lesion should be soundly healed, the lymph nodes enlarged but strictly operable, and the age and general health of the patient satisfactory for a major surgical operation. Ninety-nine of Cade's 365 cases (27% absolute, or 31% determinate—that is, when the total number of cases was reduced by excluding those which, without recurrence of cancer, had been untraced or had died from other causes) were free from disease from 5 to 15 years later. From the Middlesex Hospital Professor B. W. Windeyer reported on 243 cases treated from 1931 to 1942, again mainly by interstitial radium in anterior lesions and teleradium in those of the posterior third. In the determinate group of 230 cases 49 patients (21.3%) survived for five years or more, but of special note were the 31 out of 70 (44.2%) five-year cures in tumours of the anterior two-thirds of the tongue without palpable lymph nodes. Dr. Constance Wood, of the Medical Research Council's radiotherapeutic research unit at the Hammersmith Hospital, discussed the technique and results of treatment with a 10-gramme radium beam apparatus with which both the primary growth and the lymph node areas were irradiated to doses of the order of 6,000 r in six weeks, without block dissection. Twenty-six per cent. of 182 patients survived five years, but apart from length of survival the value of palliative treatment is shown by the fact that patients not only lived longer but their lives were rendered more comfortable.

There will be general agreement with Dr. Wood that "the proportion of cases of cancer of the tongue successfully treated by irradiation is sufficient to encourage a concerted effort being made to improve radically on the present level of achievement." Considerations other than physical dosage are involved, and the fundamental problem is essentially one of radiobiology. Already much has been done by Dr. Wood and her colleagues[5] on such problems as failure of radiotherapy due to the persistence of precancerous lesions and the importance of radiation-induced cell differentiation in sterilizing tumour tissue. Further advance on these lines seems likely to be of both clinical and biological importance.

KINGSTON APPEAL

The dispute over the closing of the Victoria Hospital at Kingston-on-Hill, Surrey, has been referred to previously in these columns.[1] The staff of the hospital put up a gallant rearguard action to defeat the decision of the regional board to take over the Victoria as a wing of the near-by county hospital. But finally they had to admit defeat. Nevertheless this defeat did not deter the general practitioners of Kingston and Malden from trying to retrieve their position. With lay sympathizers they have decided to try to found a new voluntary hospital in which they can continue to do the work they formerly used to do at the Victoria. They believe that they can convert, without much structural alteration, one of the several large mansions in the district which no longer can be used as private houses. To finance this they are appealing for funds to the people of Kingston and Malden who need the hospital, to the general public, and to the medical profession. As Dr. F. B. Lake, chairman of the Kingston and Malden Victoria Medical Foundation, points out in a letter in this week's correspondence columns, they are encouraged to make this appeal because of the wider implication of what is a local matter. In his letter he draws attention to the fact that regional boards control too wide an area to be aware of the needs of particular institutions and districts. He challenges the system by which large hospitals become governed by remote control. The appeal which is going out to members of the medical profession is published in the *Supplement*, and the story of the Victoria Hospital is there cogently told. Those who are behind the Kingston and Malden Victoria Medical Foundation make it plain that this venture of theirs is not in opposition to the National Health Service, and they are confident that their suggestions are practical—that they can do what they are setting out to do, given reasonable support.

Those who view the hospital position as a whole may disapprove of this action. But those who like to see in this country manifestations of initiative and voluntary enterprise may well see in this move on the part of the general practitioners of Kingston and Malden a lively example of this. Room for voluntary effort is much narrowed by the National Health Service, and forces which may widen this will be welcomed by those who have a sense of the great value of voluntary energies devoted to the public good. But what is of first importance behind the attitude and proposed action of the general practitioners of Kingston and Malden is their

[1] *British Medical Journal*, 1951, 1, 309 and 1028; *Supplement to the British Medical Journal*, 1951, 1, 73, 198, and 234.

concern with the place of the general practitioner in the hospital life of this country. It is this which gives the local issue a wider significance. There can be no doubt that the future of general practice is bound up more closely than ever before with its relation to hospital work. If general practitioners are either excluded from hospital work or discouraged from taking part in it, then the future of general practice will be black indeed.

JUDGMENT ON A.C.T.H.

The recent conference at Harrogate (see p. 790) was the first opportunity for clinicians in this country to exchange their experience of A.C.T.H. There was considerable uniformity in the results reported by different observers, but it is too early as yet for any final judgment to be passed. The suppression of active rheumatoid arthritis by A.C.T.H. has ceased to be a dramatic experiment and become a recognized therapy. Adequate dosage at the earliest possible moment in the acute case gives the best results. After the initial response maintenance therapy must be employed to prevent relapse. For this the repeated injection of A.C.T.H. has not the convenience of oral cortisone. But if cortisone is given for a long time it may be wise to maintain adrenal activity by repeated short courses of A.C.T.H.

Physiotherapy still remains of prime importance, however, in treating rheumatoid arthritis, while results of hormone treatment in rheumatic fever have not been outstanding: the superiority of A.C.T.H. over salicylates has yet to be proved, and prevention of permanent cardiac damage must be the criterion on which it is judged. Long-term clinical trials will settle this point, and these are already under way.

In diffuse collagen disease the fundamental question is whether or not suppression of symptoms and signs is accompanied by alteration in the natural history of the disease. Renal lesions in disseminated lupus erythematosus have failed to respond to A.C.T.H. despite considerable improvement in the skin lesions and decrease in constitutional disturbance. Moreover, the creatinuria characteristic of the disease is not abolished. This may point to a continuation of the basic disease process along its natural course while A.C.T.H. removes the usual clinical signs. Because the effect of A.C.T.H. is thus temporary rather than permanent it is most valuable in self-limiting conditions such as status asthmaticus. Decisive relief here is usually obtained by A.C.T.H., especially given intravenously, when other remedies have failed.

British results of A.C.T.H. therapy in blood diseases have been disappointing compared with some American reports. Gluco-corticoids cause the disappearance of lymphoid tissue, but they do not alter the natural history of lymphoid reticulosis. It is also interesting to note that anaphylactoid purpura has failed to respond to the hormone.

The benefits and complications of therapy are directly dependent on the fact that A.C.T.H. stimulates the adrenals to hyperactivity. It therefore finds a direct physiological application in the treatment of Simmonds's disease. Relatively small doses of A.C.T.H. are required to restore the inactive adrenal to normal function, and the clinical response is excellent. In particular the dangerous tendency to hypoglycaemia is abolished.

The conference made it clear that clinical experience has outrun basic research. The urgent need is experimental work to elucidate what pathological processes are affected by A.C.T.H. and by what mechanism. Until these fundamentals are known A.C.T.H. remains a potent weapon which must be handled with care.

BEEF AND BISCUITS

Francophiles have a habit of describing the gargantuan meals enjoyed by the French. Their claims are attested by a sample group of French working-class families who spent over half their total income on food. A similar group in England during the last quarter of 1948 spent less than a third on it. These and other interesting figures were recently published by the Institute of Statistics at Oxford.[1] The French families, over half of whom lived in Paris and the rest in the three provincial industrial towns of St. Etienne, Lille, and Marseilles, returned detailed accounts of the way they spent their money in one selected week to the Institut National de la Statistique et des Études Economiques and the Institut National d'Hygiène. The weekly accounts were adjusted to allow for expenses incurred over a longer period, such as clothing and fuel. An investigation on similar lines was carried out in this country, and the results have been compared.

Fifty-two per cent. of the French incomes were devoted to food, and 31.9% of the English. On the other hand the English spent eight times more money than the French on rent. The English outlay on fuel was also relatively higher, being double the French. Differences in climate as well as habits may be said to account for the latter, as the French climate is on the whole milder, and so the need for domestic heating is less; as a nation the French tend to lead a more open-air life than we do, and also to go to bed and get up earlier. The great majority of French workers live in flats, whereas many English people own or are purchasing their own houses; also rents in France are based on a very much lower assessment, even since the 1948 revisions.

But the most striking discrepancy lies in the amount of money spent on food. Some of this may be due to the fact that rationing was still in existence in Britain at the time of the investigations, and it must also be remembered that many staple foods in England were, and still are, subsidized, whereas prices in France are virtually uncontrolled. But the fact remains that the French families spent considerably more on food than the English and also bought different types of food. They ate, for instance, nearly twice as much meat and fats, more fresh fruit, and more bread. On the other

[1] "Household Expenditure in France and in England," *Bulletin*, 13, 229, Institute of Statistics, Oxford, 1951.

hand, they bought less fish. The English ate three times as many cakes and biscuits. Probably on account of the strict rationing, they also ate many more meals in restaurants, spending 6.8% of their weekly incomes on meals eaten away from home, while the French spent only 2% in this way. As far as could be ascertained, the calorific value of the food was fairly equal, though the French registered a substantially higher intake of animal protein.

CONTROL OF V.D. IN THE UNITED STATES

About two years ago a Syphilis Study Commission appointed by the World Health Organization visited the U.S.A. in order to evaluate the V.D. control methods in use there and particularly the penicillin treatment of syphilis. The Commission's report[1] is comprehensive and gives a good picture of the development of the campaign against V.D. Reporting of cases was first started in 1912 in the State of California. In 1918 a Venereal Disease Control Act was passed, and it was amended in 1936. This Act created a division of V.D. in the U.S. Public Health Service the functions of which were to study the cause, prevention, and treatment of V.D., to promote co-operation with State health departments, and to prevent and control the spread of V.D. by inter-State movement of infected persons. In 1948 over $31m. was allocated as V.D. grants, and much of this sum was spent on research. Great efforts are being made, by advertising and formal education, to inform both the profession and the public about the control of V.D., but such education is inevitably a slow process. Professional prostitution increased between 1944 and 1948 in spite of the May Act of 1941 and of the fact that legislation for its control exists in most States. Contact investigation has proved an effective and relatively inexpensive case-finding procedure; training of staff for this work is very thorough in the U.S.A., but education of the public is a necessary preliminary.

The Commission found that there had been an overall decrease in the number of cases of syphilis in all stages since 1947 and a progressive decline in primary and secondary syphilis following the post-war peak. Laboratory facilities for the diagnosis and control of syphilis are freely available in all States, and standards are generally high; much research is being done, particularly in the larger centres, and serum tests are constantly being improved. A nation-wide evaluation of the various methods employed is held periodically, and by this means the less efficient are discovered and the necessary improvement encouraged. In 1948 there were 3,000 diagnostic and treatment centres, and at these no patient with syphilis is denied treatment because of inability to pay, yet the fact that the Commission found that approximately half of all cases of V.D. are treated by private practitioners suggests that free treatment is not so readily available in the U.S.A. as it was in England even before the National Health Service came into being. Results of penicillin therapy in early syphilis have been closely studied, and no fewer than 45 schedules (a few including bismuth or arsenic or both, in addition to penicillin) have been tried and failure rates estimated, though the problem of distinguishing between relapse and reinfection is still unsolved. It may be that a relatively large proportion of failures, especially with rapid treatment schedules, are in fact reinfections, and if this is the case treatment with penicillin may be even more effective than published figures have suggested. Routine serum testing of expectant mothers is the most effective method of preventing congenital syphilis, and the education of private practitioners, midwives, and expectant mothers is essential if the best results are to be attained. Treatment of the mother should consist of at least 4 mega units of penicillin, and some members of the Commission thought bismuth should be given as well. Opinion was divided on whether a pregnant woman who had been treated with penicillin should be re-treated during a subsequent pregnancy, but it was agreed that the withholding of treatment in such cases should be done only for research purposes.

The V.D.-control programme in the U.S.A. might well provide a pattern which other nations could copy. The Commission's report gives some information on the cost of such activities as well as on the racial and socio-economic problems involved. Conditions, of course, differ in different countries, and few countries could afford to spend as much per head of population or per patient with venereal disease as the U.S.A. No doubt W.H.O., as it has done and is doing, will come to the aid of those countries whose need is greatest. The countries which have been most successful in their anti-V.D. campaigns are the Scandinavian countries and Great Britain. Where the standards of living are low V.D. still presents a serious problem. Public education is a necessary preliminary to a successful campaign, but this is a long-term policy; and, where the incidence of V.D. is high, mass treatment, particularly with penicillin, seems to be both practicable and to offer the greatest hope of success. The "one-shot" method of treatment with penicillin will cure up to 90% of cases of gonorrhoea, and recent reports[2,3] suggest that it may do the same in early syphilis. Nevertheless this alone will never eradicate V.D. entirely, and nothing short of international co-operation, perhaps under the aegis of W.H.O., can offer hope of a full measure of success.

[1] *Venereal Disease Control in the U.S.A., W.H.O. Tech. Rep. Ser. No* 15, 1950, Geneva.
[2] Thomas, E. W., Rein, C. R., Landy, S., and Kitchen, D. K., *Amer. J. Syph.*, 1950, **34**, 331.
[3] Willcox, R. R., *Med. World, Lond.*, 1950, **72**, 518.

The half-yearly indexes to Volume I of the *Journal* and the *Supplement* for 1951 are now being sent to members who receive them regularly and to subscribers. Members who have not previously asked for the indexes to be sent regularly to them can obtain copies, post free, on application to the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1. Those wishing to receive the indexes regularly as published should mention this.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

MEDICAL RELIEF OF PAIN

BY

E. J. WAYNE, M.D., F.R.C.P.

Professor of Pharmacology and Therapeutics, University of Sheffield; Physician, United Sheffield Hospitals

Pain is the commonest symptom for which a patient seeks advice, and a practitioner is often judged by the extent to which his treatment provides relief. It is, of course, only justifiable to treat pain symptomatically after every attempt has been made to discover its cause. The conditions which give rise to pain are many, but the mechanisms through which they act are comparatively few. Thus pain may arise in smooth muscle either from spasm or from overstretching. It may be caused by direct pressure on various parts of the nervous system. But perhaps the commonest cause is the direct irritation of nerve endings by chemical substances, such as hydrochloric acid in peptic ulcer or Lewis's P factor in muscle ischaemia. Clearly, different methods of treatment must be adopted in these different instances, and when the exciting cause is known it is often possible to use specific remedies. Thus spasmolytic drugs such as belladonna may bring relief to the sufferer from a spastic colon, and nitroglycerin remains the best remedy in the treatment and prophylaxis of attacks of angina of effort. Pain due to bacterial inflammation can usually be removed by the appropriate chemotherapeutic agent.

Unfortunately, however, in many cases the exciting cause cannot be discovered, and even when it can be found non-specific treatment may be the only practicable form of therapy, as, for example, in an attack of myocardial infarction or in inoperable carcinoma of the lung. It is then that the practitioner turns to drugs which depress the central mechanism for the appreciation of pain, and it is with these that I shall mainly deal.

Physical Methods for the Relief of Pain

Nevertheless, the more simple physical methods and the group of counter-irritant drugs should not be forgotten. It is quite easy to apply heat in the home by using hot-water bottles, electric blankets, or the ordinary bowl type of electric fire; the greater relief afforded by the more elaborate methods used in departments devoted to physiotherapy is often in part due to psychological mechanisms. It should be remembered that the application of cold sometimes gives greater relief than that of heat, and an ice-cold compress or an evaporating lotion may be worth a trial in treating bruises or sprains.

Counter-irritant drugs are less used now than formerly, but they give undoubted relief in appropriate cases—for example, painful lesions in muscles, tendons, and joints. It will be appreciated that they all act through essentially the same mechanism—the release of histamine or some closely allied substance—and they differ chiefly in the intensity and duration of their action. It therefore seems reasonable to choose those substances which do not cause serious damage to the skin and which are relatively cheap. There is no evidence that liniments containing aconite, belladonna, or opium have any analgesic action on unbroken skin, and the simple liniments such as linimentum saponis *B.P.*, linimentum album *B.P.C.*, and linimentum methylis salicylatis *B.P.C.* are all satisfactory preparations. The black ointment unguentum iodi denigrescens cum methylis salicylatis of the *National Formulary* has in addition to a counter-irritant action an impressive colour and smell.

The slightly soluble local analgesics such as benzocaine and orthocaine can be applied either as powders or ointments—for example, unguentum benzocainae co. *B.P.C.*—to superficial painful lesions such as ulcers, fissures, and mucous surfaces, but their action is short-lived and they may tend to retard healing. Sometimes they lead to a sensitization dermatitis.

An injection of procaine hydrochloride (as injectio procainae et adrenalinae mitis *B.P.*) into a localized area of tenderness in cases of non-articular "rheumatism" or tennis-elbow gives relief which may persist long after the action of the analgesic has worn off.

Use of Analgesic Drugs

In choosing from the large number of available preparations the practitioner must take into account the severity of the pain, as it is desirable wherever possible to use the less powerful drugs, for it is an unfortunate fact that the really potent analgesics all possess a tendency to habit formation.

Relative Efficiency of Analgesics.—Many methods have been used to test the relative efficiency of analgesic drugs, and it is perhaps not surprising that different results are obtained in the hands of different workers. Observations on animals in the laboratory are valuable as "sighting" tests, and information from human volunteers subjected to painful stimuli of varying intensity has added much to our knowledge of the mechanism of the relief of pain. Nevertheless, the clinician is bound to be more impressed by results obtained in human beings suffering from pain. The most striking finding which comes from observations in this field is that inert tablets and injections may be effective pain relievers. Indeed, in one trial inert tablets gave some degree of relief in 50% of patients suffering from pain of mild to moderate severity. Such results are not necessarily due to suggestion; they may be a measure of the tendency of pain to come and go, and the credit is thus given to whatever remedy is being taken at the time.

Choice of an Analgesic.—This usually lies between a member of the antipyretic group such as aspirin, a member of the narcotic group to which morphine belongs, and one of the newer analgesics—pethidine, amidone ("physeptone"), and phenadoxone ("heptalgin"). For severe pain such as that which arises from myocardial infarction or advanced malignant disease there is no fully satisfactory alternative to morphine. It is a remarkable fact that this drug, which was first isolated in 1816, is still the most widely used analgesic. It has a capacity to distract the attention and relieve anxiety possessed by no other substance. The effect resembles in some ways that of leucotomy; indeed, morphine has been said to produce a "reversible pharmacological leucotomy." The newer analgesics relieve

pain effectively, but do not possess the sedative effect of morphine. It is clear that there are circumstances in which this is desirable, but most patients with severe pain prefer an opiate. The antipyretic analgesics are far less effective pain relievers, and presumably act at a different point in the central nervous system, for they produce neither euphoria nor addiction. Their safety is, in fact, their chief recommendation.

Antipyretic Group of Analgesics

A number of phenol derivatives have the property of reducing temperature and relieving pain, especially pain of so-called "rheumatic" type. They have no sedative effect and are not hypnotics, though they may induce sleep by suggestion. If, however, it is desired to produce sleep with certainty a hypnotic should be used in addition.

Aspirin.—In 1937 the annual consumption of this drug in the U.S.A. was 7,000,000,000 5-gr. (0.32-g.) tablets, and it is surprising that toxic effects are so seldom seen. In patients who have an idiosyncrasy to the drug, urticaria or asthma may be produced. Heavy dosage in anyone will give rise to tinnitus, deafness, nausea, or vomiting. On an empty stomach it may cause indigestion or even superficial erosion of the gastric mucosa. The tablets should therefore be taken crushed after food or in a soluble form. Prolonged use of aspirin and other salicylates may lead to hypoprothrombinaemia and the risk of haemorrhage.

Phenacetin is a useful alternative to aspirin because it does not irritate the gastric mucosa. Rarely it may cause methaemoglobinaemia and cyanosis.

Amidopyrine is the most powerful member of the group and is still widely used on the continent of Europe. It can, however, give rise to agranulocytosis, and though the risk is small it should not be undertaken. It is unfortunately still a constituent of some proprietary analgesic tablets.

Sodium salicylate is unpalatable and is a relatively ineffective analgesic except in acute rheumatism. In this condition it should be given in large doses—for example, 90 to 180 gr. (6 to 12 g.) a day.

Morphine Group of Alkaloids

Morphine has certain drawbacks, but in spite of these it is still the most widely used member of the group. At least 30% of individuals experience nausea after its use and more than 10% vomit. It may give rise to constipation, and full doses easily produce respiratory depression.

Diamorphine (*heroin*) should be used with great caution. The maximum pharmacological dose of ⅛ gr. (8 mg.) is equivalent to more than ¼ gr. (32 mg.) of morphine. It gives rise to less vomiting or constipation than morphine but to much greater euphoria. Its liability to cause addiction has led to a complete prohibition of its importation and manufacture in the U.S.A., and its use in this country could be with advantage reduced and restricted to parenteral administration.

Dihydromorphinone ("*dilaudid*") has less sedative action than morphine, and its duration of action is shorter. It has the merit of causing less nausea than morphine, and is useful in conditions such as myocardial infarction and abdominal emergencies where the emetic action of morphine is especially undesirable. It is very apt to cause addiction. The usual dose in the adult is 1/32 to 1/16 gr. (2 to 4 mg.).

Codeine is a safe drug and is very unlikely to produce addiction. It rarely gives rise to vomiting, but may constipate. It is unfortunately a weak analgesic even when given in full doses of 1 gr. (65 mg.), and its main use is as a depressant to the cough centre.

Methyl dihydromorphinone ("*metopon*") has recently come into prominence in the U.S.A. and may become available in this country. Its great advantage is that it has less tendency than morphine to produce alimentary symptoms and mental dullness. Tolerance and dependence develop less rapidly, and it is effective when given orally. Its use should be restricted to cases with severe pain—for example, terminal cancer. It is apt to cause severe respiratory depression. The oral dose is 1/10 to 1/7 gr. (6 to 9 mg.).

Papaveretum and similar proprietary preparations—for example, "omnopon"—consist of mixtures of the purified alkaloids of crude opium. Controlled trials showed no difference between their effects and those of morphine.

The Newer Analgesics

Several new synthetic analgesics have been discovered in recent years. Only those which are available in this country are described.

Pethidine ("*dolantin*," "*demerol*," "*meperidine*" *U.S.P.*). This substance has a definite analgesic action, the intensity of its effect lying between that of the aromatic analgesics and of morphine. It has a slight local analgesic action, and drowsiness may occur after full doses. It has an antispasmodic effect on smooth muscle, and it is the combination of this action with its capacity to depress the perception of pain that makes it specially valuable in intestinal colic. It may, however, be used to relieve pain of any type, and has been widely employed in obstetric practice and pre- and post-operatively. It is less likely than morphine to produce unpleasant side-effects, but with doses of 100 mg. or more many patients complain of dizziness, nausea, or sweating. In prolonged overdosage or acute poisoning atropine-like effects predominate—for example, dilated pupils, dry mouth, tachycardia, and convulsions. There is, however, a wide margin of safety. Although a dose of 25 mg. (⅜ gr.) will often give an effect, the usual certainly effective dose is 100 mg. (1½ gr.). The duration of its action is less than that of morphine, but it is advisable that not more than 6 gr. (400 mg.) should be given in 24 hours. Tolerance does not easily develop, but an increasing number of cases of addiction have been reported, and it has been included with drugs scheduled under the Dangerous Drugs Act.

Amidone ("*physeptone*," "*methadon*," "*miadone*," "*dolophine*").—This is an effective analgesic with approximately the same pain-relieving effect as morphine, so that 10 mg. (1/6 gr.) is roughly equivalent to 10 mg. (1/6 gr.) of morphine. There is, however, considerable individual variation in response, and single doses as high as ½ gr. (32 mg.) may be given. It differs from morphine chiefly in that it has a lesser tendency to produce nausea and vomiting and that it gives rise to less mental dullness. These may be great advantages, but the narcotic effect of morphine is sometimes desirable, and can be partly imitated by combining the drug with a short-acting barbiturate. Amidone is of value in most forms of pain, especially if the patient wishes to remain in full possession of his faculties. Its side-effects are, in order of frequency, dizziness, nausea, dryness of the mouth, sweating, and mental depression. They occur in about 10% of patients and are much commoner in individuals

who are not confined to bed. Amidone has a depressant action on the respiratory and cough centres, and often controls cough in doses as low as 2 mg. (1/30 gr.). It has a small margin of safety, and its use in children, especially as an elixir, is undesirable. For the relief of pain a dose of 5 mg. (1/12 gr.) should be tried initially, but the usual effective dose is 10 mg. (1/6 gr.). Addiction is less likely than with pethidine, but can occur. It has been shown that amidone will alleviate the symptoms of morphine withdrawal. It also has been included in the drugs scheduled under the Dangerous Drugs Act.

Phenadoxone (*heptalgin*).—This drug is chemically closely related to amidone, and tests based on its capacity to relieve the pain of muscle ischaemia indicate that it is at least as active an analgesic, weight for weight. Clinical experience, however, suggests that it is less effective. It has not been as fully investigated as amidone, but it seems probable that it has fewer side-effects, although in full doses it causes drowsiness. It is said to be less depressant to the respiratory centre. Phenadoxone is given orally in doses of 5 to 30 mg. (1/12 to ¼ gr.) or by injection in doses of 10 mg. (1/6 gr.). It should be combined with a barbiturate if sedation is required, and it should not usually be given to patients who are out of bed. Phenadoxone gives rise to mild euphoria, but so far addiction has not been reported. It is scheduled under the Dangerous Drugs Act.

Combinations of Analgesic Drugs

There is probably no other field of therapy in which the phenomenon of alleged synergism has been so widely exploited by the manufacturers of proprietary remedies. Combinations of the antipyretic analgesics may sometimes be justified, since their toxic effects are different, and it is conceivable that the addition of caffeine or codeine may enhance the efficiency of the preparation. One such preparation—the compound tablet of codeine *B.P.C.*—is an imitation of a well-known proprietary remedy. It contains 4 gr. (0.26 g.) each of aspirin and phenacetin and ⅛ gr. (8 mg.) of codeine phosphate. It should be noted that the compound tablet of codeine contains in two tablets a greater total dose of analgesic than three tablets of aspirin or phenacetin; the alleged greater efficiency of this and other preparations over that of aspirin may be merely a question of dosage.

As pain is so often accompanied by insomnia, it is not surprising that many attempts have been made to imitate the action of morphine by combining the aromatic analgesics with barbiturates. These themselves have a very poor analgesic effect unless given in doses sufficient to cause unconsciousness, although there is some evidence that they may potentiate the pain-relieving actions of analgesics. The objections to such preparations are twofold: (1) some contain amidopyrine as the analgesic constituent; and (2) the barbiturate is often one of the longer-acting group, such as barbitone itself, and as the effect of the analgesic is as a rule short-lived, and the dose therefore often repeated, a cumulative effect may easily occur. It is always preferable to administer the analgesic and the hypnotic separately, so that the dose of the former can be repeated without necessarily at the same time giving a further dose of hypnotic.

Conclusion

The practitioner has thus a very wide choice of therapeutic methods when faced with the problem of pain. Those who wish to explore for themselves the newer analgesics would be well advised to try amidone or phenadoxone by mouth as an alternative to morphine. The evening dose can be accompanied by a barbiturate. Such treatment may allow the patient to remain relatively aware of his surroundings during the daytime, and there is only a slight danger of producing addiction. Constipation is less likely to occur than with morphine. Pethidine is specially valuable in cases with smooth-muscle spasm and in obstetric practice. It now seems unlikely that a satisfactory alternative to morphine will be discovered which does not tend to give addiction. It is, however, probable that substances may yet be discovered which have fewer side-effects than the present analgesics and thus may approximate more closely to the "ideal analgesic" of the pharmacologist.

EUROPEAN COMMITTEE FOR MENTAL HYGIENE

The seventh conference of the European Committee for Mental Hygiene was held at Vevey, Switzerland, from August 30 to September 3. Dr. André Répond, the Director of the Mental Health Services for the Canton of Valais and past president of the World Federation for Mental Health, presided. This was the first conference to be held since the war, the last having taken place at Lugano in June, 1939. There were some 70 members and delegates from 13 countries, including Great Britain, Italy, Austria, and Western Germany. On the first day representatives from the 13 countries gave an account of the mental health services in their countries, and on the second day reports dealing with the special problems of mental hygiene occurring in various groups of countries were presented by Dr. Doris Odlum for the English-speaking countries, Dr. Y. Porc'her (Paris) for the Latin countries, Professor Dr. H. Schulte (Bremen) for Central Europe, and Professor P. Reiter (Copenhagen) for Scandinavia.

Dr. RONALD HARGREAVES, the chief of the Mental Health Section of the World Health Organization, gave a brief report on the concept of mental hygiene in that organization. In W.H.O. they held the view that mental hygiene could play the same role in the sphere of mental health and disease as physical hygiene played in the physical sphere. The doctor's role in mental as in physical hygiene was to treat the sick and to make researches into the nature and causes of mental illness and mental deficiency. The reduction of the incidence of mental disorders of all kinds and of mental deficiency could be achieved only through the activities of those who were dealing with the causative conditions in the general population—that is to say, public health authorities, teachers, ministers of religion, and, indeed, all those who dealt with the development and welfare of other human beings.

Geographical Variation in Incidence of Psychoses

As a result of special surveys it had been found that in Italy, although there was a high consumption of alcohol, there was a very low incidence of alcoholic psychosis, but this was not the case in certain other European countries. In Northern Sweden there was a high incidence of schizophrenia in relation to other psychoses, whereas in South Sweden manic-depressive psychoses predominated. In tribalized Africans, only the men have manic-depressive psychosis, and even this usually occurs only in those who are doing jobs of the kind that are usually carried out by and in association with white men. Even the limited amount of research which had already been undertaken showed how greatly the problems varied between country and country, and how essential it was to understand the fundamental causes and the contributory factors before either advocating or taking measures to deal with them. By means of child psychiatry and developmental psychology it might be possible to discover these basic factors. From the point of view of

prevention it was of little good studying the fully fledged conditions. Edward Glover had truly said that Waterloo was planned in the nurseries of Corsica.

Resolutions and Future Work

The reports were followed by an interesting and lively discussion. Resolutions were passed unanimously urging that education in the principles and the application of mental hygiene should be as widespread as possible and, in the first place, should be addressed to special groups (including the medical profession, educationists, nurses, psychologists and social workers, the clergy, public health officials, magistrates, and judges), and, secondly, recording the view, based on evidence from the delegates, that guidance and advice for those about to marry and for expectant mothers, child guidance clinics, and clinical and advisory facilities for adults in the field of mental health had proved the most efficacious services in preventing nervous and mental disorders and character deviations.

After the conference an administrative session was held, at which it was decided to reconstitute the existing organization. The new body would be called "The European League for Mental Hygiene," and be composed of national associations for mental health, each country to have one voting delegate who would hold the office of vice-president of the league. Seventeen countries had already applied for membership, including those represented at the meeting—namely, Austria, Belgium, Denmark, Eire, France, Finland, Western Germany, Great Britain, Greece, Holland, Italy, Luxembourg, and Switzerland. Dr. Répond was elected as president and Dr. H. Bersot as secretary-treasurer. Dr. Doris Odlum was appointed president-elect. Dr. Bersot undertook to arrange for the publication of a report of the congress, including the full text of papers read at the meetings and an account of the discussions.

CONFERENCE ON A.C.T.H.

A conference on A.C.T.H., arranged by the Armour Laboratories (the United Kingdom subsidiary of Armour and Co., Chicago, and makers of a brand of A.C.T.H.), was held at Harrogate on September 13 and 14. The conference was attended by over 100 physicians and surgeons, all of whom had had practical experience of the use of A.C.T.H. The members were given a reception by Councillor N. A. Foster, Mayor of Harrogate, and Mr. A. M. Fletcher, managing director of the company. After dinner two films on the physiology and use of A.C.T.H. were shown.

Control of Dosage

The conference was opened by the first chairman, Dr. F. T. G. Prunty (London).

Dr. O. JANUS (Manchester) described the eosinopenic response to A.C.T.H. He considered this to be a good test of adrenal function. By using a careful technique the test could be put on a quantitative basis. A prolonged study of four normal subjects had shown that there was an individual variation in response to a standard dose of A.C.T.H. A similar variation was seen among patients treated with A.C.T.H. There was not always a correlation between the clinical response and the response to test doses of cortisone and A.C.T.H. Dr. C. L. COPE (London) had also found a variable adrenal response to A.C.T.H., as shown by bio-assay of cortisone and compound F in urine.

Dr. A. SLESSOR (Glasgow) said the aim of therapy was to give enough A.C.T.H. to flood the body with an excess of adrenal hormones, without causing undesirable metabolic side-effects. Retention of salt and water, muscle weakness from potassium loss, the appearance of Cushing's syndrome, liability to thrombosis, and priapism in the male occurred with high doses. A.C.T.H. therapy might be dangerous in the presence of tuberculosis, psychosis, diabetes, chronic nephritis, or heart failure. Daily weighing and blood-pressure readings and frequent eosinophil counts were most useful in following therapy. The use of serial E.C.G.s was a good way of detecting significant potassium loss. Dr. R. R. H. LOVELL (London) said that each patient needed a certain dose of A.C.T.H. to suppress his disease. Sometimes this critical dose would be one which also gave rise to harmful side-effects. Other speakers agreed with this concept of a critical dose for each patient and each disease process. Dr. COPE (London) pointed out that the eosinophil count could rise in the presence of adequate adrenal stimulation; repeated counts had a limited value in assessing treatment.

Gastro-intestinal Disease

Dr. J. R. FORBES (Wrexham) said that he had found no change in gastric acid secretion after A.C.T.H. There was some evidence to show that pepsin secretion might be increased. He had given a course of A.C.T.H. to five patients with gastric ulcers, but there had been no significant change in their condition. There were reports of peptic ulcers perforating during A.C.T.H. therapy. He did not think that A.C.T.H. had been proved to be the cause of perforation, but it had certainly masked the clinical picture when perforation occurred.

Five cases of ulcerative colitis had been given A.C.T.H. No clear picture of definite benefit was found, but Dr. Forbes thought that the usual progress towards healing might have been accelerated. Several other speakers had had similar experiences with ulcerative colitis. On occasion there had been a dramatic clinical improvement with A.C.T.H., but usually there was little change. One case of perforated peptic ulcer during A.C.T.H. therapy was described and one case of severe melaena. Dr. D. H. MACQUAIDE (Northampton) said that he had found that A.C.T.H. increased the capacity for fat absorption in cases of steatorrhoea.

Asthma and Dermatomyositis

Professor F. J. NATTRASS and Dr. A. L. LATNER (Newcastle) stressed the difficulty of assessing any therapy in asthma. Of 13 cases in status asthmaticus A.C.T.H. (25 mg. six-hourly) had led to decisive clinical improvement. Three of seven cases of chronic continuous asthma had shown similar improvement. They considered that A.C.T.H. was no substitute for the intelligent use of adrenaline, but if that failed in status asthmaticus A.C.T.H. should be given forthwith. The immediate results of short-term therapy were impressive, but the use of A.C.T.H. did not lead to long-term remissions. Dr. S. JOHNSSON (Sweden) described eight patients in whom he had obtained similar results. In the discussion it was considered that the intravenous route was the most effective for A.C.T.H. therapy in status asthmaticus.

Dr. D. V. HUBBLE (Derby) described the vicissitudes of a single case of acute dermatomyositis treated with intravenous A.C.T.H. given daily over an eight-hour period. Oedema tended to occur when the drip had been running for some time, and at one stage he thought the patient had an allergic response to the A.C.T.H. Dr. B. WOLMAN (Manchester) said that "neptal" was useful when low-salt diets had failed to prevent oedema. Dr. E. N. ALLOTT (London) considered that it was more efficient to keep the intravenous dose running for 24 hours rather than a shorter period.

Simmonds's Disease

Mr. J. M. Johnston was in the chair for the second session.

Dr. F. DUDLEY HART (London) described the treatment of five cases of Simmonds's disease with short courses of A.C.T.H. There was considerable clinical improvement, especially freedom from hypoglycaemia. The improvement was maintained for about three months after the course. Dr. T. A. CHALMERS (London) had found a similar improvement in five cases, and noted that the poor diuretic response to water became normal after A.C.T.H. Dr. JANUS (Manchester) said that a single injection of A.C.T.H. produced no eosinopenic response in Simmonds's disease, but small doses of cortisone produced a marked eosinopenia.

Rheumatic Fever

Dr. E. G. L. BYWATERS (Taplow) described a carefully controlled study of rheumatic fever. It was not possible as yet to assess any long-term results. A.C.T.H. appeared to suppress symptoms, but if the disease was still active

when treatment was discontinued symptoms recurred. He also described experiments on the spreading effects of hyaluronidase. This was inhibited by A.C.T.H. but not by cortisone. In rheumatic fever the body took an abnormally long time to reconstitute its barrier against the spreading effect. This was not altered by A.C.T.H. Dr. W. G. WELCH (London) said that he was impressed by the quick suppression of symptoms in rheumatic fever by A.C.T.H. Dr. H. E. CLUXTON (Armour Laboratories, Chicago) said that intravenous A.C.T.H. gave better results. The aim must be to start treatment at the earliest possible moment and to give an effective dose.

Hypoglycaemia and Rheumatoid Arthritis

Dr. G. D. KERSLEY and L. MANDEL (Bath) described the good clinical response to hypoglycaemia in a large number of patients with rheumatoid arthritis. The reaction to hypoglycaemia did not always parallel that to cortisone and A.C.T.H. They also described two cases of rheumatoid arthritis which failed to respond to A.C.T.H., and considered that investigation of these rare failures might give a clue to the action of adrenal hormones. Dr. D. A. LONG (London) had found in his experimental work on guinea-pigs that slight deficiency of thyroxin or ascorbic acid might result in failure of A.C.T.H. action. He suggested that these factors could be applicable to the human.

Blood Diseases

Dr. W. S. C. Copeman was in the chair for the third session.

Professor L. J. WITTS (Oxford) said that there had been reports of temporary remission in 60% to 70% of cases of acute leukaemia treated with A.C.T.H. However, the great majority relapsed and proved refractory to further therapy. Acute monocytic leukaemia did not respond. Chronic leukaemias did not benefit from A.C.T.H. Hodgkin's disease had failed to improve. Sarcoidosis might show improvement when acute exacerbations were treated, but not otherwise. Loeffler's syndrome had responded in some instances. In his own experience he had found no therapeutic benefit from A.C.T.H. in congenital haemolytic anaemia, haemoglobinuria, thrombocytopenic purpura, and anaphylactoid purpura. Episodes of bleeding in thrombocytopenia might be stopped despite no change in the platelet count. He attributed this to a rise in capillary resistance. Acquired haemolytic anaemias did show improvement on occasion, but results had been disappointing. Rare cases of resistant anaemias appeared to respond. Dr. R. W. LUXTON (Manchester) reported seven cases of lymphoid reticulosis treated by A.C.T.H. with no benefit. He considered that malignant change in one case might have been caused by A.C.T.H. Other speakers reported experience similar to that of Professor Witts. Dr. KERSLEY said that the anaemia of rheumatoid arthritis did not respond to A.C.T.H., and other speakers reported the same observation.

Capillary Resistance and Adrenocortical Activity

Dr. J. J. R. DUTHIE and Dr. H. N. ROBSON (Edinburgh) described their work on the variation in capillary resistance with adrenocortical activity. Alarming stimuli, cortisone, and A.C.T.H. all increased capillary resistance. Many other steroid hormones had been found to have no effect. But in rheumatoid arthritis the resistance was lowered by deoxycortone in large doses. They concluded that adrenal activity increased capillary resistance by the action of 11-oxysteroids. The paper was followed by a detailed discussion of the significance of these results and the possible mechanisms involved.

Pituitary-adrenocortical Activity in Burns

Dr. S. SEVITT (Birmingham) gave a detailed account of eosinopenia following burns. He considered this to indicate adrenal activity. The duration of eosinopenia was related to the extent of the burn. Analysis of fatal burns had shown that the great majority of cases died with active adrenals, as shown by eosinopenia. The eosinopenic response to adrenaline when patients were recovering from burns might be poor in those with mental instability. Dr. COPE (London) said that he had investigated adrenal function in fatal medical conditions, and did not think that adrenal exhaustion was a factor, except in overwhelming infections. Dr. LONG (London) made a plea for the closer study of the mechanism of adrenal steroid action in cells.

Lupus Erythematosus

Dr. F. T. G. PRUNTY (London) gave a detailed account of eight cases treated with A.C.T.H. Acute manifestations of lupus erythematosus could be suppressed, but repeated short courses appeared to have little effect on the natural history of the disease. Renal involvement was uninfluenced by A.C.T.H. He demonstrated suppression of granulation tissue formation by A.C.T.H. in one case. The effect of A.C.T.H. on scleroderma was not impressive. The creatinuria of these diseases was not abolished by A.C.T.H. Dr. BYWATERS (Taplow) quoted his experience and agreed with Dr. Prunty's conclusions. Dr. J. R. NASSIM (London) reported three cases of disseminated lupus, and considered that one had developed tuberculosis while on A.C.T.H.

A.C.T.H. in Rheumatoid Arthritis

Professor F. S. Nattrass was in the chair for the last session.

Dr. B. WOLMAN (Manchester) had used the eosinopenic response to A.C.T.H. as an indication of adrenal activity in the first day of life. The majority of full-term and premature babies showed a normal response in the first day of life. Failure to respond until the second day of life, or even later, appeared to be correlated with a low birth weight. He reviewed the available literature on the subject.

Dr. W. S. C. COPEMAN (London) and Dr. O. A. SAVAGE (London) discussed various difficulties in the management of cases of rheumatoid arthritis. All their cases had made a clinical response to A.C.T.H., and in only one, who developed a temporary severe diabetes, were there significant side-effects. The average initial daily dose (divided into four injections) was 120 mg. Smaller doses had proved ineffective. The lowest maintenance dose was 40 mg. daily (in four injections). Intravenous A.C.T.H. had proved useful when the response to intramuscular therapy was poor, but a large number of veins appeared to be thrombosed by this. The progress of treatment was assessed by a carefully laid down clinical routine. The patient's euphoria made the subjective assessment of improvement faulty. It was impossible to forecast what the effective dose of A.C.T.H. would be in any case. Dr. J. GOSLINGS (Leyden) reviewed his experience. He had found lower doses (40 mg. daily) to be effective in the initial course. He described work on cases in which the rheumatoid arthritis had relapsed despite continued treatment. There was no evidence of hypothyroidism in these cases, as judged by radio-iodine tests, and the addition of ascorbic acid to the treatment had made no difference. No antibodies to A.C.T.H. had been found in the blood. Dr. D. K. BRIGGS (Paris) was impressed by the dramatic improvement of his patients who had been bedridden. Continuous therapy appeared to be necessary.

Recent American Experience

Dr. H. E. CLUXTON (Armour Laboratories, Chicago) summed up the work of the conference, and reviewed the basic physiology of A.C.T.H. He pointed out that cortisone caused adrenal atrophy, while A.C.T.H. stimulated the adrenals. He said that the answers to the action of adrenal steroids would be found by the study of cell enzymes, and that much work was being done on the subject. Recent American experience led him to believe that A.C.T.H. would be of increasing value to the surgeon in combating post-operative conditions. A.C.T.H. in combination with streptomycin and P.A.S. appeared to be of great use in tuberculous meningitis and renal tuberculosis. Eye conditions responded very well, and A.C.T.H. was promising in the treatment of diabetic retinitis. He stressed the importance of preventing potassium depletion, and the giving of thyroid with long-

term therapy. Correct use of antibiotics was essential if infection occurred when A.C.T.H. was being used. In any disease treatment must be begun early, in adequate dosage, and then continued on a maintenance dose. When stopping therapy a slow diminution of dosage should always be carried out.

His remarks were widely discussed, and he answered many questions on the points he had raised.

MEDICAL DEFENCE UNION

The 66th annual general meeting of the Medical Defence Union was held in its new council chamber at Tavistock House South on September 18. The chair was taken by the acting president, Mr. St. J. D. Buxton, who referred with much regret to the death of Mr. Ivor Back, whereby the Union had been deprived of the services of a president of outstanding personality. The council had asked him (Mr. Buxton) to fill the chair for the remainder of the term.

Mr. Buxton then proceeded to review the work of the year. The Medical Act had been in operation for some months, and the first few cases had appeared before the Disciplinary Committee of the General Medical Council. There was a right of appeal from the Committee's decision to the Judicial Committee of the Privy Council, and the Union appreciated its duty to assist any member who, having just cause for complaint, desired to take advantage of this procedure. In the ordinary work of the Union 195 cases during the year had been referred to the solicitor; 61 of these involved allegations of professional negligence, but 37 were withdrawn or abandoned, and, of the five that came to trial, four were decided in favour of the practitioner. It was considered necessary to take to the House of Lords one case of negligence alleged against a member (the late Mr. J. B. Hunter), and the House of Lords found in his favour and so ended satisfactorily a matter which caused grave distress to an experienced surgeon and serious concern to the medical profession.

No year passed without a report of a retained swab and of complications in plaster-of-Paris splinting for fractures and in the sequelae of intravenous injections. Injury to the brachial plexus from erroneous positioning of the arm was also occurring rather frequently. On the question of ethical matters and disputes, when these were referred to the Union it was usual to advise the member, if he was a member of the British Medical Association, to use the machinery of the Association rather than refer to the courts, thus avoiding publicity which would often be considerable in the area of the practice.

It was reported that the membership of the Union was approaching 36,000, and that there were over 300 overseas members. The treasurer, Dr. Henry Robinson, presented the financial report, which showed a surplus of income over expenditure amounting to nearly £13,000. This replaced a deficit for the two previous years, the improved result being due to the raising of the subscription from £1 to £2.

The report was adopted, and Mr. E. D. D. Davis, Dr. H. Rivers Pollock, and Mr. D. G. C. Tasker, who retired by rotation, were re-elected to the council. Permission was given for the necessary amendment of the memorandum and articles to permit admission to membership of those on the register for "provisionally registered practitioners"; under the new Medical Act this register exists side by side with that for fully registered practitioners. On the motion of Dr. Peter Macdonald a hearty vote of thanks was accorded to the acting president for his services.

Immediately following the annual general meeting there was a meeting of the elected members of the council, at which Dr. S. Cochrane Shanks was appointed president of the Union for the year 1951–2. Dr. Shanks has been a member of the council for some years and also a member of its executive and finance committees. Dr. Robinson was reappointed treasurer, and Mr. Tasker chairman of the executive committee.

RECRUITMENT AND TRAINING OF NURSES

BRITISH NURSES EXAMINE REPORT OF W.H.O. EXPERT COMMITTEE

The World Health Organization appointed an expert committee on nursing which held its first session in Geneva last year. Its terms of reference are to advise the World Health Assembly on measures to ensure the recruitment of nurses in proportion to the needs of each country and on measures to give nurses a training in keeping with the numerous and complicated tasks devolving upon them. The report and recommendations of the first session of the expert committee were the subject of a conference in London, summoned by the Royal College of Nursing, on September 14, and attended by 250 nurses from home and overseas. Dr. BROCK CHISHOLM, director-general of W.H.O., touched on the great disparities between different countries in nursing provision and status. Some countries had no trained nurses; in many parts of the world the training was insufficient. In some places nursing was a despised profession, and this problem had to be faced before anything constructive could be done about instruction in techniques. The task of W.H.O. was to help in taking the steps most appropriate to each country.

Work of the Expert Committee

Miss MARY LAMBIE, of New Zealand, who had presided over the first session of the expert committee, said that the committee had decided that the provision of an adequate number of nurses of suitable quality required the enlistment of candidates of all types for training, the promotion of the most effective use of the various types of nursing personnel, and the provision of educational facilities. A pilot study had been organized in co-operation with the Rockefeller Foundation with a view to determining, in different communities, how nursing could best function to meet the real health needs through health teaching, participation in preventive programmes, care of the sick, family visiting, and other methods. In some countries W.H.O. had been asked to assist in establishing a nursing division, which was done through W.H.O. regional offices, and in other countries the organization itself took the initiative in appointing such divisions. It was learned that the International Labour Organization had been asked to make a study of working and living conditions of nurses throughout the world, and the expert committee, having already recommended that such a study be made, thought it advisable that the work should be undertaken in conjunction with the I.L.O. A comparative study of the various types of nursing training in Equatorial Africa was also recommended, but no action has so far been taken because the W.H.O. regional office for Africa had been created only after the recent assembly in May, 1951.

Miss Lambie also stated that the expert committee had drawn attention to the need for reviewing basic education programmes, even in highly organized countries, to ensure that the continuous development of health work was incorporated in the curriculums. Post-basic (postgraduate) education of nurses had also been considered, and the International Council of Nurses had been asked to make a study of the available programmes of post-basic education throughout the world and to prepare a guide for the furtherance of such programmes. This work would actually be carried out by the Florence Nightingale International Foundation, which is now associated with the International Council, in conjunction with the national nursing associations. At the same time a study of basic education for nursing would be made.

Later in the conference, under the leadership of Miss F. N. Udell, chief nursing officer, Colonial Office, the practical application in Great Britain of the expert committee's recommendations, and the ways in which the British nursing profession could help, were discussed.

THE KING'S HEALTH

OPERATION FOR LUNG RESECTION

Below we print the bulletins which have been issued since the King's illness in May. The first was made public on Friday, June 1, and read:

The King has been confined to his room for the past week with an attack of influenza.

There is now a small area of catarrhal inflammation in the lung, but the constitutional disturbance is slight.

DANIEL DAVIES. GEOFFREY MARSHALL.
HORACE EVANS. JOHN WEIR.

On Monday, June 4, the next bulletin stated:

The catarrhal inflammation in the King's lung has not entirely disappeared, though his Majesty's general condition has improved.

A period of complete rest will be essential to his Majesty's recovery, and on the advice of his doctors he has reluctantly decided to cancel all his public engagements for at least four weeks.

DANIEL DAVIES. GEOFFREY MARSHALL.
HORACE EVANS. JOHN WEIR.

A further bulletin issued on Wednesday, June 6, read:

The King's progress both in the local and general condition continues to be satisfactory.

DANIEL DAVIES. GEOFFREY MARSHALL.
HORACE EVANS. JOHN WEIR.

A bulletin issued on Tuesday, June 12, stated:

The King continues to make good progress. The temperature has been normal for the past week, and the inflammation in the lung has subsided.

In view of the attacks of catarrhal infection his Majesty has suffered this year we have advised that a prolonged convalescence is essential.

DANIEL DAVIES. GEOFFREY MARSHALL.
HORACE EVANS. JOHN WEIR.

The next bulletin was issued on Tuesday, September 18:

During the King's recent illness a series of examinations have been carried out, including radiology and bronchoscopy. These investigations now show structural changes to have developed in the lung. His Majesty has been advised to stay in London for further treatment.

G. MATHER CORDINER. GEOFFREY MARSHALL.
DANIEL DAVIES. C. PRICE THOMAS.
THOMAS DUNHILL. JOHN WEIR.
PETER KERLEY. ROBERT A. YOUNG.

A bulletin on Friday, September 21, stated:

The condition of the King's lung gives cause for concern.

In view of the structural changes referred to in the last bulletin we have advised his Majesty to undergo an operation in the near future. This advice the King has accepted.

DANIEL DAVIES. C. PRICE THOMAS.
GEOFFREY MARSHALL. HORACE EVANS.
ROBERT A. YOUNG. JOHN WEIR.
THOMAS DUNHILL.

At 4.30 p.m. on Sunday, September 23, a bulletin was issued which stated:

The King underwent an operation for lung resection this morning. Whilst anxiety must remain for some days, his Majesty's immediate post-operative condition is satisfactory.

DANIEL DAVIES. C. PRICE THOMAS.
GEOFFREY MARSHALL. R. MACHRAY.
ROBERT A. YOUNG. HORACE EVANS.
THOMAS DUNHILL. JOHN WEIR.

Later on the same day, at 9.15 p.m., a further bulletin stated:

The King's condition continues to be as satisfactory as can be expected.

DANIEL DAVIES. JOHN WEIR.
GEOFFREY MARSHALL. C. PRICE THOMAS.
HORACE EVANS.

A bulletin issued on Monday, September 24, stated:

The King has had a restful night. His Majesty's condition this morning continues to be as satisfactory as can be expected.

DANIEL DAVIES. JOHN WEIR.
HORACE EVANS. C. PRICE THOMAS.
GEOFFREY MARSHALL.

A second bulletin, issued on the same day at 7 p.m., stated:

The King has gained strength during the day.

DANIEL DAVIES. C. PRICE THOMAS.
HORACE EVANS. JOHN WEIR.
GEOFFREY MARSHALL.

The latest bulletin before going to press, issued at 11 a.m. on Tuesday, September 25, stated:

After another restful night the King continues to gain strength.

DANIEL DAVIES. C. PRICE THOMAS.
HORACE EVANS. JOHN WEIR.
GEOFFREY MARSHALL.

GENERAL ELECTION

MEDICAL CANDIDATES

In 1950 at the last General Election 32 medical men and women stood as candidates and 10 were elected. According to the information at present obtainable the following 13 members of the medical profession will be standing for Parliament at the General Election on October 25.

The names of those who were Members of the last Parliament are indicated by an asterisk. It is not possible in all cases to give the age of the candidates, but the year of their qualification affords some guidance, and this has been given in parentheses.

*REGINALD FREDERICK BRITTAIN BENNETT, V.R.D., Gosport and Fareham, Conservative. (1937).

M.P. for Gosport and Fareham since February, 1950. Psychiatrist for South Hampshire. Formerly Psychiatric Registrar, Maudsley Hospital; Member, Inner Temple; Surgeon Lieutenant-Commander, R.N.V.R.

*ALFRED DAVIES DEVONSHER BROUGHTON, Batley and Morley, Labour. (1929).

M.P. for Batley and Morley since February, 1949. Honorary Physician, Batley and District Hospital. Former Chairman of Dewsbury Division of B.M.A. Squadron Leader, R.A.F.V.R.

*Rt. Hon. WALTER ELLIOT ELLIOT, P.C., *M.C.*, Kelvingrove Conservative. (1913).

Was Minister of Health, 1938–40, and had previously been Secretary of State for Scotland and Minister of Agriculture. M.P. for Lanark, 1918–23; Kelvingrove, 1924–45; Scottish Universities, 1946–50; and Kelvingrove since 1950. Rector of University of Glasgow from November, 1946, to 1950, and Rector of University of Aberdeen for 1933–6. Won *M.C.* and bar in first world war.

*SOMERVILLE HASTINGS, Barking, Labour. (1902).

M.P. for Reading, 1923–4 and 1929–31, and for Barking since 1945. Consulting Surgeon and Lecturer to Ear and Throat

Department, Middlesex Hospital. President, Socialist Medical Association. Chairman of Board of Governors of Hammersmith, West London, and St. Mark's Hospitals Group. Chairman of London County Council, 1944–5, and previously chairman of its Hospitals and Medical Services Committee.

*CHARLES HILL, Luton, Liberal-Conservative. (1927).

M.P. for Luton since February, 1950. Secretary, British Medical Association, 1944–50. President, World Medical Association, 1949–50. Vice-president, and formerly chairman, Central Council for Health Education.

BERNARD HOMA, Hendon South, Labour. (1922).

In general practice. Honorary Anaesthetist, German Hospital, Dalston.

*SANTO WAYBURN JEGER, Holborn and St. Pancras South, Labour (1923).

M.P. for St. Pancras South-East from 1945 to 1950; Holborn and St. Pancras South from 1950. Practises in London and has taken a prominent part in local government in Shoreditch.

*HYACINTH BERNARD WENCESLAUS MORGAN, Warrington, Labour. (1909).

Advisory medical officer, Union of Post Office Workers, and adviser and consulting specialist, industrial diseases, Trades Union Congress. M.P. for Warrington since February, 1950; previously sat for Camberwell North-West and Rochdale. Member, B.M.A. Council.

DYFRIG HUWS PENNANT, D.S.O., Pembroke, Liberal. (1912).

Member, Welsh Regional Hospital Board; Chairman, Carmarthen Mental Hospitals Group; Examiner and Honorary Life Member of the Order of St. John of Jerusalem. Former Chairman of South-West Wales Division of B.M.A.

*MALCOLM STODDART-SCOTT, O.B.E., T.D., Ripon, Conservative (1926).

M.P. for Ripon since February, 1950; previously sat for Pudsey and Otley. On medical staff of General Infirmary at Leeds, 1929–39. A.D.M.S. 48th Division, 1943–5. Chairman, British Rheumatic Association.

*BARNET STROSS, Stoke-on-Trent Central, Labour. (1925).

M.P. for Hanley Division of Stoke-on-Trent from 1945 to 1950; Central Division since 1950. General practitioner, Stoke-on-Trent.

*Rt. Hon. EDITH CLARA SUMMERSKILL, P.C., Fulham West, Labour. (1924).

M.P. since 1938 and Parliamentary Secretary to the Ministry of Food from 1945 to 1950, when she was appointed Minister of National Insurance.

JOHN RICHARD TIMMIS TURNER, Crewe, Conservative. (1936).

General practitioner, Nantwich.

Correspondence

New Voluntary Hospital for Kingston

SIR,—In the next few days most doctors in active practice will receive a letter (see *Supplement*, page 126) asking them to subscribe to the foundation of a new voluntary hospital for Kingston and Malden. We are emboldened to address this appeal to the whole medical profession for the reason that, although the immediate issue is a local one, the implications of the scheme may affect doctors everywhere.

Before 1948 large hospitals, both municipal and voluntary, were managed by bodies of local citizens who were aware of local conditions and needs, and who usually gave due weight to the views of their medical staffs. In addition, most rural and a large number of urban areas possessed hospitals of the cottage type where general practitioners could attend their own patients. We in Kingston had a hospital which had developed a little further from the latter class, in that it had a full consultant staff holding regular sessions and functioned in all respects as a general hospital, save that instead of residents the routine care of the patients was in the hands of their general practitioners. Its closure after a remarkable struggle to preserve it was deplored by the whole district.

There seems no reason why these arrangements should not have continued under nationalization, but in fact the hospital services are controlled by regional boards governing far too wide an area to be cognizant of the needs of particular institutions and districts, assisted by group management committees—nominated, not elected, bodies—who, judging by our own group, are permitted to have very little real power.

At the same time, as larger hospitals become governed by remote control the smaller ones seem destined to cease to exist, and, since they are the only places where the two great divisions of medicine—hospital and general practice—meet and truly collaborate, this would seem to be a most retrograde step.

If we succeed, as we have every confidence we shall, in making the Kingston and Malden Victoria Hospital rise from its ashes on a voluntary basis, we shall have established the principle that such hospitals ought to exist, set up a model which might well be copied in future developments of the National Health Service, and might even initiate administrative reforms that would make a healthier Health Service everywhere.

Cheques may be sent to the Hon. Treasurer, Dr. Desmond de Launay, 9, Coombe Rise, Kingston Hill, Surrey.—I am, etc.,

Kingston-on-Thames. F. B. LAKE.

Sulphamerazine Dangerous

SIR,—I was very interested in Dr. E. C. Atkinson's letter (September 15, p. 674). Since January, 1951, at the Department of Child Health, Cardiff, we have had four cases of haematuria with oliguria or anuria following the use of a sulphamerazine suspension. Brief details of these cases are given:

Case 1.—A girl aged 5 years developed respiratory infection. Given the suspension for six days before admission: dose two teaspoonfuls twice daily. Child drank little. Day before admission passed small amount of blood-stained urine. Almost complete anuria for two days. As no urine was obtained until diuresis started, sulphonamide crystals were never seen.

Case 2.—A boy aged 2 years 8 months. Given the suspension for bronchitis. Dose, one teaspoonful four-hourly for four days. Two days before admission passed blood in urine, but drug continued for a further two days. Developed anuria for two days. Urine contained many sulphonamide crystals. Blood urea rose to 70 mg. %.

Case 3.—A boy aged 4½ years. Given the suspension during the initial phase of measles. His mother used an old bottle of the medicine which she says was "rather thick at the bottom." Haematuria and oliguria developed.

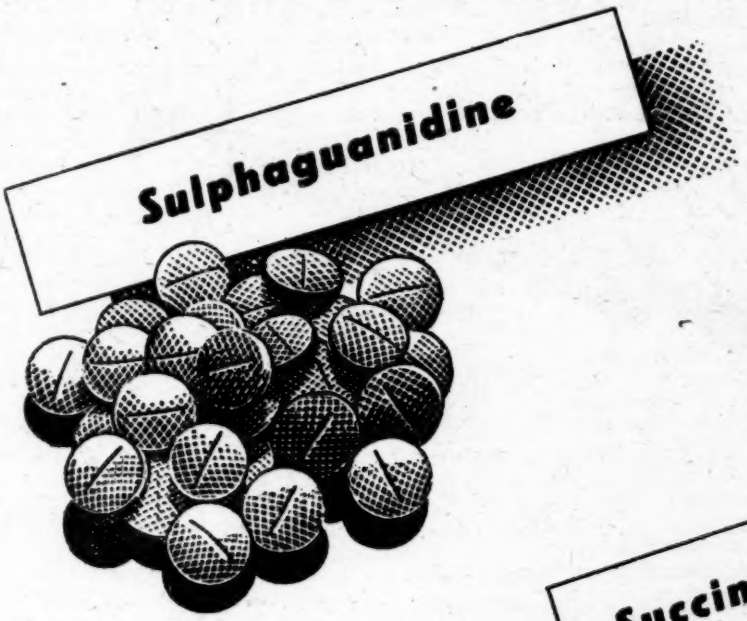
Case 4.—A boy aged 6½ years. Given the suspension for a respiratory infection. He developed haematuria and oliguria.

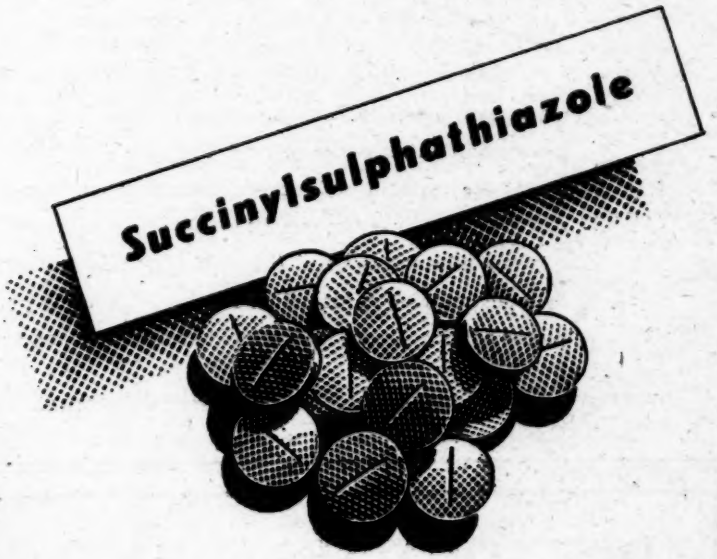
Despite the manufacturers' clear instructions that for children the drug should be given at 12-hourly intervals, it is often prescribed more frequently. Also, sick children often have a poor fluid intake with consequent danger of urinary concentration; and failure to shake the bottle well results in the last doses being stronger than they should be. I can therefore support Dr. Atkinson's plea that the use of sulphamerazine suspensions should be queried when there are safe alternatives available.—I am, etc.,

Cardiff. JOHN RENDLE-SHORT.

SIR,—I was particularly interested to read Dr. E. C. Atkinson's letter on the dangers of sulphamerazine (September 15, p. 674), in view of the fact that only the night before I had been called out to deal with the following case. I had been treating a well-developed woman of 45 for *B. coli* cystitis with sulphamerazine. She had received an initial dose of 2 g. and thereafter a six-hourly dose of 1 g., which was continued for five days. Forty-eight hours after taking the last dose she was seized with violent pain in her right inguinal region passing backwards into her lumbar region, suggesting the passage of a renal calculus. Next morning the right kidney was a little tender on palpation. There was no history of a previous attack. I have no doubt that her symptoms were due to the passage of crystals of sulphamerazine, and that, had this occurred on a somewhat larger scale, symptoms of ureteric block would have supervened.—I am, etc.,

London, S.W.7. NIGEL LORING.





maximal *efficacy with* smaller *dosage*

provides an efficient method of controlling the infection in bacillary dysentery and other gastro-intestinal conditions of bacterial origin. It has the advantages over sulphaguanidine and succinylsulphathiazole of higher bacteriostatic activity in the bowel and is thus usually effective in smaller dosage. **Supplies:** Containers of 25, 100 and 500 x 0·50 Gm. tablets.

We shall be glad to send detailed literature on request

manufactured by

MAY & BAKER LTD

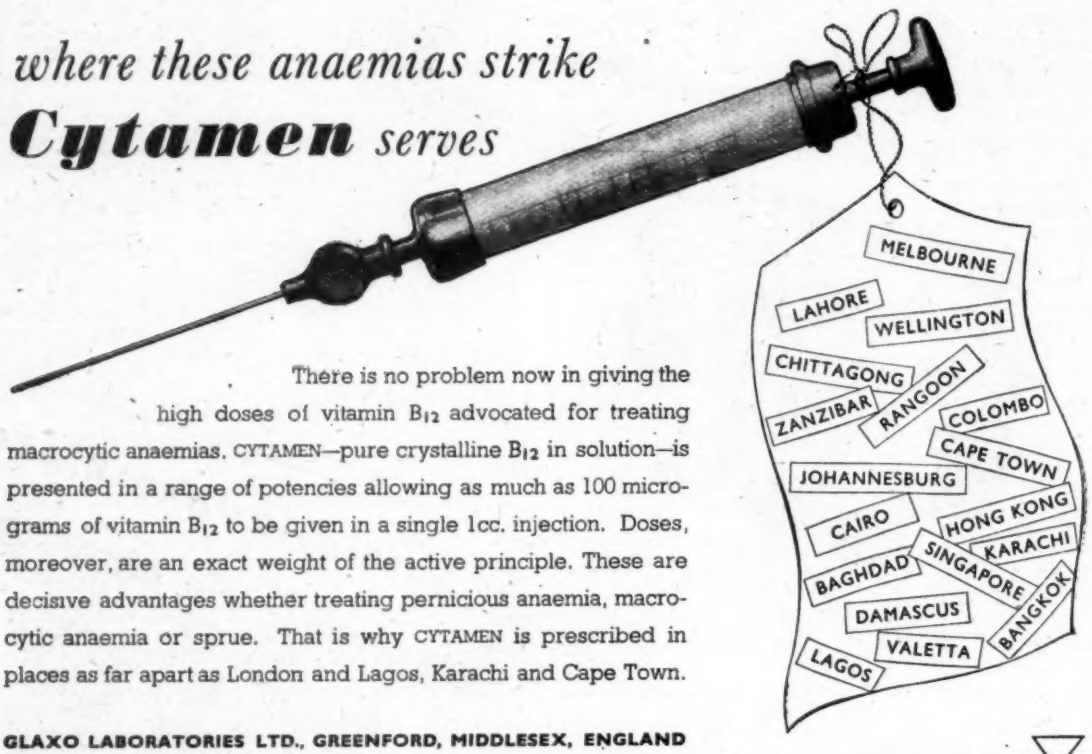
MA183

distributors **PHARMACEUTICAL SPECIALITIES (MAY & BAKER) LTD DAGENHAM**

PERNICIOUS ANAEMIA · TROPICAL MACROCYTIC ANAEMIA · SPRUE

where these anaemias strike

Cytamen *serves*



There is no problem now in giving the high doses of vitamin B_{12} advocated for treating macrocytic anaemias. CYTAMEN—pure crystalline B_{12} in solution—is presented in a range of potencies allowing as much as 100 micrograms of vitamin B_{12} to be given in a single 1cc. injection. Doses, moreover, are an exact weight of the active principle. These are decisive advantages whether treating pernicious anaemia, macrocytic anaemia or sprue. That is why CYTAMEN is prescribed in places as far apart as London and Lagos, Karachi and Cape Town.

GLAXO LABORATORIES LTD., GREENFORD, MIDDLESEX, ENGLAND

Research Laboratories : Manufacturers of Medical products and foods. Associate companies or agents in almost every country in the world

'DISTAQUAINE' G
brand

Dry substance consisting of procaine penicillin and suspending agents for the extemporaneous preparation of an aqueous suspension for intramuscular injection.

'DISTAQUAINE' *FORTIFIED*
brand

Dry substance consisting of procaine penicillin plus potassium penicillin and suspending agents for the preparation of an aqueous suspension. The inclusion of the potassium salt provides an immediately accessible dose of soluble penicillin in addition to the prolonged action of the more slowly absorbed procaine salt.

'DISTAQUAINE' *SUSPENSION*
brand

'Distaquaine' G in ready prepared aqueous suspension, an additional convenience for the busy practitioner.

Distributed by :
ALLEN & HANBURYS LTD.
BRITISH DRUG HOUSES LTD.
BURROUGHS WELLCOME & CO.
EVANS MEDICAL SUPPLIES LTD.
IMPERIAL CHEMICAL (PHARMACEUTICALS) LTD.
PHARMACEUTICAL SPECIALITIES (MAY & BAKER), LTD.

Advantages of 'DISTAQUAINE' brand preparations

- *Aqueous, containing neither oil nor wax*
- *Easy to prepare and administer*
- *Least possible pain on injection*
- *Effective blood levels up to 24 hours following administration*
- *Dry syringe unnecessary*
- *Equipment easily cleaned after use*

THE DISTILLERS COMPANY (BIOCHEMICALS) LIMITED

SPEKE LIVERPOOL

'DISTAQUAINE', trade mark, is the property of the manufacturers

Cortisone and A.C.T.H. in Hypopituitarism

SIR,—The stimulating article (September 8, p. 564) by Dr. V. K. Summers and Professor H. L. Sheehan raises several interesting points. It is noteworthy that cortisone therapy proved beneficial in their hands, clinical improvement lasting for 12 to 15 days after stopping the drug. There seems little doubt but that cortisone is proving effective in ameliorating the clinical picture in this distressing condition. Their experience with A.C.T.H. appears, however, to have been much less happy, both patients developing severe headaches within the first seven days of therapy, one passing into coma for a period of five hours and subsequently becoming hemiplegic for some days.

I have now given seven courses of A.C.T.H. to five patients with this condition, total dosage averaging 310 mg. given six-hourly intramuscuarly over a period of one to two weeks, and one six-day course of intravenous therapy, dosage totalling 120 mg. Since starting these clinical trials in January last I have not seen the therapeutic complications noted above, and progress on and after therapy has been satisfactory, clinical improvement lasting at least four weeks after therapy in each case and usually longer than six. In this condition only small doses need to be given; I am inclined to think that even smaller doses than I have been giving may give equally good results. Thorn and his associates (*New Engl. J. Med.*, 1950, **242**, 783) state that patients may be maintained in excellent general condition on a relatively small dosage, 5–10 mg. every 6 to 12 hours being sufficient. I would therefore like to range my eight uneventful satisfactory courses of treatment with A.C.T.H. against the two reported by the above authors, as I find from conversation with colleagues who have also treated these cases with A.C.T.H. in similar and larger doses that uncomplicated improvement is the rule in most cases.—I am, etc.,

London, W.1. F. DUDLEY HART.

Penalties for Sexual Offences

SIR,—Correspondence on this subject, like that on its near relatives corporal punishment, capital punishment, and the psychopathic personality, is unequalled for becoming circular. The sample published in your issue of September 15 (pp. 672–3) is a good example of this, in that the familiar tussle between the would-be medical man, the moralist, and the man with the simple practical solution is well represented. The issue common to all these subjects is whether we do, or do not, regard "perverted" behaviour as being symptomatic of illness. Because it touches on this issue, Dr. H. Osmond's letter, though it may overrate the purely organic aspect, is a more satisfying answer to Dr. H. Ward-Smith's indignation than is Dr. G. W. Fleming's own spirited rejoinder. The correspondence might be more fruitful if, instead of mixing the issues, contributors would choose between discussing the medical point of view and that of the moralist.

If perversion is considered to be a medical subject, the first need that strikes one is that of more exact knowledge. Does castration, for example, reduce the likelihood of perverted behaviour? Proof of this is not impressive, and the Danish experiment has thrown little light on this point. In the present state of knowledge, the suggestion of castration followed by psychotherapy is strongly opposed by many psychotherapists, who feel that even the harmless requirement, under the Criminal Justice Act, of compulsory treatment is a great handicap in therapy. It is difficult to conclude that castration owes its appeal, as a suggestion, to anything other than its punitive quality. Our ignorance is such that, while no man of sensibility doubts that homosexual seduction is a bad thing for an adolescent boy, strict medical evidence on this point remains very obscure.

If the moral issue be considered paramount the letters of Dr. Ward-Smith and Dr. G. Orissa Taylor become more truly relevant; but doctors writing as moralists are unlikely to add much to the enormous literature through many centuries on the ethics of the subject. However, even strong religious feelings should not make one overlook the fact that the punishment meted out to the man in question was not unusual in its severity, that public opinion is far from silent, and that all but a small proportion of the population approve of such savage penalties being awarded from time to time in our courts. No practising overt homosexual man capable of thought can escape the knowledge that discovery means utter disgrace and ruin and that betrayal is the rule rather than the exception. The fact that such knowledge is such an indifferent deterrent suggests that pathological processes of the mind are involved.

The community would benefit from greater unity in the medical profession on this subject. If perversion is a medical subject it is worthy of study using all the resources of modern scientific method, so that we may equip the jurists with instruments more effective than crude punishment to use in the common task. If the moralists are to continue to mould public opinion without medicine considering itself to be involved, we must at least stop misleading the courts into the belief that medical treatment will help. In such a case the medical profession must be prepared to stand on one side and leave the field clear to those who are able to bring scientific method to its study. The least we can do is to clarify our correspondence on these subjects in our journals.—I am, etc.,

London, W.1. KENNETH SODDY.

SIR,—Dr. G. W. Fleming (August 11, p. 363) and Dr. H. Ward-Smith (September 1, p. 549) appear to present two extremes of view. It is impossible to pronounce judgment on the matter without knowing the actual facts of the case, and these are not reported. Whatever the facts, the offence was either a misdemeanour or a felony, and the punishment was 18 months' imprisonment and deprivation of pension.

By all means let the rear-admiral be imprisoned and, if possible, subjected at the same time to psychiatric treatment. The deprivation of pension, however, is another matter and has wide implications. The capital sum necessary to produce a pension of £1,000 per annum is something in the neighbourhood of £33,000. It follows therefore that in addition to the prison sentence the admiral has been fined £33,000 or, alternatively, £1,000 per annum for the rest of his life. If he is married and has a family (unlikely but possible) his wife and children have also been punished for his offence, which is quite unjust. Would the State in the case of any other citizen who had amassed a capital sum of £33,000 by his past labours and who had committed the same offence fine him such a sum? Certainly not. To this extent therefore the sentence is out of proportion to the crime and is a double sentence for the same offence.

A pension is defined in my dictionary as "a stated allowance to a person in consideration of past services; a yearly sum granted by Government to retired public officers." It is in fact deferred pay. Instead of allowing a man to make provision for his retirement by paying him so that he can do so the State sets aside a certain sum to provide a pension for him. This is what the National Health Service does. A most pertinent point therefore arises. Are doctors, employed in any branch of the National Health Service, "public officers"? In the years to come will some unfortunate doctor who has been convicted of a misdemeanour or a felony (and it is the conviction, not the nature of the offence, which, I understand, determines the deprivation) be mulcted of all the deferred pay his lifelong labours have earned him?—I am, etc.,

Harrow, Middlesex. J. B. WRATHALL ROWE.

SIR,—I would suggest that the need to study the problem scientifically, and to support the work that the Institute for the Scientific Treatment of Delinquency is doing, is greater than the search for a punishment that fits the crime. Public opinion has not advanced as rapidly as we like to think.

Thirty years ago A was sentenced to 18 months' imprisonment for an offence against a young girl, his daughter. One year ago, his son, B, was sent to prison for five years for assaulting a young girl, who was A's grand-daughter and also sexually precocious. B may not have been a good man, but he was not a wholly bad man. Six months previously he appealed desperately for medical help and was in fact sent to hospital in the hope that he would be helped and society protected. This did not reduce his sentence, nor has he received the promised treatment in prison to date. B has lost his house, his job, his pension, and maybe his wife. What of the third generation, C? One is already known to be sexually precocious. B's four children have to be maintained by the State in institutions which, like prisons, foster homosexuality and behaviour difficulties. Can the law and medicine not do better than this? Surely society has mishandled the problem of sexual offenders in the past and the time has come for scientific study and prevention.—I am, etc.,

Colchester. H. N. DAVY.

*** This correspondence is now closed.—ED., *B.M.J.*

Legal Termination of Pregnancy

SIR,—We have read with interest ("Any Questions?" September 8, p. 622) the very clear answer to a question on legal termination of pregnancy in Britain. It may interest your readers to learn that in Sweden new legislative measures have been introduced widening the scope of their law. The present Swedish Abortion Act became effective in 1939, and has been amended several times, most recently in 1946.

Under the Act, legal abortions are permitted on certain specified medical, socio-medical, humanitarian, and eugenic indications. Abortion on medical grounds is permitted when the birth of a child would endanger the mother's life, owing to sickness, malformation, or general weakness of the woman. A socio-medical indication exists when, "in view of the woman's living conditions and other circumstances, it may be anticipated that her physical or mental strength would be seriously impaired by the birth and care of the child." Humanitarian reasons apply when the pregnancy has resulted from rape or other unlawful coercion or certain sex crimes. Eugenic indication for lawful abortion exists whenever it is anticipated that the child by inheritance will be insane, imbecilic, or seriously handicapped by sickness or malformation. When the woman is a carrier of such inheritance she must generally undergo sterilization.

Permission for legal abortion is granted by the socio-psychiatric committee of the Medical Board, made up of a rapporteur representing the board, two members appointed by the Government, and two deputy members. Except in cases of eugenic indication and when the woman is declared mentally incompetent, abortion may be carried out without reference to the committee if, in the opinion of a medical officer in consultation with the physician performing the operation, it is considered necessary. In emergency cases, any practitioner is permitted to perform an abortion without consulting a medical officer or referring the case to the medical board.

The number of legal abortions has increased considerably in recent years, particularly since the amendment of the Act in 1946, when the socio-medical indication was added. The number of criminal abortions, however, appear to have diminished since then. Sweden has thus reformed her law, and, from the many desperate appeals for personal help we receive from women (and from men on their behalf), we believe that it is urgently necessary in this country to widen the range of indications for legal termination of pregnancy.—We are, etc.,

London, W.2.

JANET CHANCE,
Chairman.

ALICE JENKINS,
Hon. Secretary.
The Abortion Law Reform Association.

Treatment of Trypanosomiasis

SIR,—Dr. K. Robertson's report (September 1, p. 546) of a case of trypanosomiasis observed in England may suggest to the inexperienced that a course of treatment with suramin alone is normally adequate when infection has already advanced to the stage where the cerebrospinal fluid shows increases of protein-content and cell-count. It should be emphasized that improvement of more than a temporary nature is exceptional at that stage of the disease unless the suramin (if used at all) is supplemented by some such drug as tryparsamide, which is known to be efficacious in late-stage trypanosomiasis. In the case described by Drs. J. E. Cates and M. B. McIlroy (August 18, p. 401), which prompted Dr. Robertson's letter, a full course of treatment by suramin alone also seemed to lead to recovery, but the patient relapsed a year later.—I am, etc.,

Oxford. E. M. LOURIE.

Referred Pain

SIR,—Dr. E. G. Herzog (September 15, p. 674) asks why we experience somatic, in addition to visceral, pain. The reason is that, if a pain is severe enough, it is felt throughout the relevant segment (Kellgren, *Clin. Sci.*, 1938, **3**, 2). It is the extent of the dermatome, not of the myotome, that governs the size of the painful area (Cyriax, *Rheumatism and Soft-tissue Injuries*, p. 42, 1947). His example of myocardial pain referred to the upper limb bears out this fact. The heart is derived from segments T 1, 2, and 3, and the first thoracic segment stretches as far as the ulnar border of the hand. Indeed, I have seen one case in which pain of myocardial origin was felt exclusively at the inner side of the elbow.

The mechanism by which pain is referred was revealed by the experiments of Woolsey, Marshall, and Bard (*J. Neurophysiol.*, 1941, **4**, 1) on monkeys. Electroencephalography showed that stimulation of a given area of skin gave rise to an electrical reaction in a fixed and minute area of cortex. Increase in the intensity of the stimulus led to a corresponding increase in the number of cortical sensory cells affected. Such spread to adjacent cells would obviously be interpreted by the patient as an enlargement of the painful area. The mosaic forming the sensory cortex is arranged dermatome by dermatome, and the extensive reaction resulting from a strong stimulus is confined within the limits of the area of cortex corresponding to that dermatome. This is the reason for the patients' common statement that at first the pain was confined to a small region—usually somewhere near its source—but spread widely within the relevant dermatome as it became more severe.—I am, etc.,

London, W.1. JAMES CYRIAX.

Tomato-skin Ileus

SIR,—Dr. J. K. Willson-Pepper's letter on a case of prune-stone ileus (July 28, p. 238) draws fresh attention to the rare but interesting and well-recognized surgical emergency of intestinal obstruction due to food. Ward-McQuaid's comprehensive paper on this subject (*British Medical Journal*, 1950, **1**, 1106) was followed by an interesting correspondence in your columns, in which various articles of diet were mentioned—a pickled onion and an orange pith (Banham, **2**, 109), pieces of grapefruit (Jackson), and a bolus of mango fibres (Gilges, **2**, 787). A recent case in which tomato-skins were to blame may perhaps be added to the list.

A man aged 76 was admitted to hospital on May 28 with a history of 48 hours' duration of acute intestinal obstruction. On examination a well-marked "ladder pattern" was present and a small swelling (of which the patient was unaware) was detected in the right femoral region. A diagnosis of strangulated Richter's femoral hernia was made, and under general anaesthesia the swelling was exposed by a horizontal incision. A small femoral hernial sac was found, empty of contents except fluid welling into it from the general peritoneal cavity. A lower right paramedian

incision was then made. Grossly distended coils of ileum presented, and these were traced down to a place in the lower ileum where the bowel was felt to contain something about the size and shape of a small hen's egg. Below this the bowel was collapsed and empty. This solid body was milked up gently from its point of impaction, the bowel was opened, and the bezoar removed from the lumen quite easily. It was found to be a friable cylindrical shaped mass with blunt ends, looking rather like a bundle of short sticks tied together; on closer inspection these sticks were seen to be tightly rolled thin skins of some fruit, probably tomato. A pathological report confirmed that there were approximately two dozen portions of vegetable material encrusted with intestinal contents—elongated rolled portions of tomato-skin measuring 3 cm. in length and varying from 1–3 mm. in diameter.

It would seem likely that the femoral hernia played some part in the obstruction, as part of the ileum probably entered the hernia, or was kinked at that point. Fluid contents passed on, but the solid elements gradually collected above it till a mass formed, and complete obstruction ensued. Vigorous peristalsis then freed the bowel (which did not show any obvious hernial constriction ring on its surface at operation) but the bezoar was by this time too large to pass on spontaneously through the narrower lumen of the terminal part of the ileum.—I am, etc.,

Edinburgh. JAMES A. ROSS.

Plasma Pentose in Pre-eclampsia

SIR,—Drs. H. N. Green, J. D. Hopewell, and C. J. Threlfall (September 8, p. 571) have advanced the theory that ischaemia of the uterus is a major aetiological factor in eclamptic states, and obstetric medicine must be indebted to them for their research. I feel that I cannot, however, agree with their integrations and would like to discuss them.

Odell and others have shown that the filtration rate in pre-eclampsia is much reduced. Adenylic acid and its derivatives (Bing *et al.*, *Amer. J. Physiol.*, 1948, **153**, 159) have been shown to lower the filtration rate and the filtration fraction. It may therefore follow that the enhanced plasma pentose value in pre-eclampsia reflects a degree of glomerular ischaemia.

If so this decreased glomerular flow is part of a vitally important though completely overlooked mechanism. Bradley *et al.* (*Amer. J. Med.*, 1950, **9**, 766) published a series of clearance figures in various renal diseases of the greatest value as they included extraction ratio determinations. Though he does not specifically detail the pre-eclamptic clearances Bradley states that they are no different from those of acute nephritis, in which disease the filtration rate and the filtration fraction are reduced together with the extraction ratio. *But a most significant concomitant is that the renal blood flow is not reduced and may even be increased.* The reduction in the extraction ratio signifies that the circulation is directed to areas where tubular function is in abeyance or to zones which are non-nephronic. Cortical ischaemia can explain this reduced extraction ratio. The increased (or normal) blood flow, because of diversion to a pathway in which renal resistance is low, is accompanied by a fall in the filtration fraction and consequent diminution in filtration rate. The juxta-medullary route must therefore be invoked.

Acute overstretching of the uterus, experimentally in rabbits, has been shown to cause a cortical shut-down, the major incident in the Oxford mechanism. The paper of Green *et al.* indirectly supports this association in man. Furthermore, sympathetic tone which contributes to the "shunt" is diminished in recumbency, and in this fact may be found an important explanation of the effects of the erect posture on the disease to which the authors allude. Neither is there doubt that tissue ischaemia is associated with a nervously integrated cortical shut-down, responsible for anti-diuretic effects. I would be deeply appreciative for information of a method evoking uterine ischaemia with subsequent rise of blood pressure in which renal influence had been excluded by denervation of the kidney and/or of the vessels supplying the uterus.

In fact, the evidence as it now accumulates heavily supports a nervously integrated cortical shut-down in the aetiology of toxaemia. That the pre-eclamptic state cannot owe its origin principally to humoral substances is indicated by the instant therapeutic effect of low spinal block. Homer Smith (*The Kidney*, 1951, p. 18) states that the renal nerve supply arises from T 4 to L 4. The dramatic release of renal spasm occurs when spinal anaesthesia reaches T 11 or 12. Lund and Cleland at the recent International Congress of Anaesthetists warmly advocated conduction anaesthesia for severe toxaemic states and produced clinical proof of its success. Cleland had noted release of renal vasospasm when the level of T 11 was reached. In view of the renal innervation and the circumstance of pregnancy the only feasible explanation of the improvement was an interrruption in the utero-renal reflex pathway, while the sudden amelioration must exclude persisting humoral toxins as major factors in the aetiology.

Overstretching evokes resistance, which I believe is the aetiological factor. Plasma pentose levels may indirectly measure the latter and serve as a prognostic and consequently a therapeutic guide in the syndrome. The data provided by the authors must prove of great value, and I congratulate them on its usefulness.—I am, etc.,

London, W.1. JOHN SOPHIAN.

Unnecessary X-ray Examinations

SIR,—I would like to compliment Dr. W. A. Bellamy (September 8, p. 611), of Aylesbury, for his very excellent letter on *x*-ray examinations. In my experience what he has said is fully borne out by the present facts. *X*-ray examinations in my departments have increased up to 40% and 60%. This can only mean one of two things: we must have been bad doctors prior to July, 1948, by omitting to radiograph this 60%; or this large increase is due, as Dr. Bellamy suggests, to lack of experience and clinical acumen. Until such experience, etc., is obtained I suppose as radiologists we shall have to put up with the overwork in our departments, but not, I hope, in silence. In any case the excessive shortage of films will soon be limiting.—I am, etc.,

London, W.1. THOS. V. CRICHLOW.

Hexamethonium in Acute Ventricular Failure

SIR,—On six separate occasions attacks of acute left ventricular failure in a hypertensive patient have been successfully treated with intravenous hexamethonium bromide. The attacks lasted half to three-quarters of an hour when treated with an injection of morphine and atropine. With hexamethonium bromide there was marked improvement within five minutes, and within ten minutes the dyspnoea was gone and the chest signs were minimal. 10 mg. was sufficient for treatment for the first attack, but now 30 to 40 mg. have to be used, 5 mg. a minute. The blood pressure dropped rapidly from 270/170 mm. Hg to 190/130 and even lower. The patient responded well to subcutaneous therapy. The blood pressure drops from the usual level of 220/140 to 160/110 after 1½ hours on regular injections. The patient has infrequent attacks now, only when very excited and when she has become tolerant to the dose being used. I hope that the above information will be of some value in the treatment of attacks of left ventricular failure.—I am, etc.,

Northwood, Middlesex. D. GLAJCHEN.

Teaching General Practice

SIR,—On a few occasions before qualification I was privileged to attend the surgery of a busy general practitioner in Liverpool and to accompany him on his rounds. I can, therefore, personally support the plea made in your annotation (August 25, p. 459) for more G.P. experience for the student.

The most important thing I learned was that general practice was not the easy job I had been led to imagine it was.

The problem of sorting out during a busy surgery those patients who were, in fact, ill and the further problem of their disposal were ones I had not encountered in hospital. Not only did I learn something of the conditions under which a mixed practice is worked and the types of patient encountered, but also received my initiation into the rite of form-filling. In addition, I saw my first cases of measles and chicken-pox—and where better to see the common infectious diseases than in general practice? Yes, Sir, a week with a G.P. is surely the minimum to be aimed at. Learning by one's mistakes is all very well, but learning to avoid them seems far better.—I am, etc.,

Southport. MYER GOLDMAN.

POINTS FROM LETTERS

Ascaris

Dr. H. S. ANDERSON writes: Mr. M. Smyth's letter (September 8, p. 609) has reminded me of an experience in 1903 when, a captain R.A.M.C., I had charge of the Followers Hospital in Rangoon Cantonment. An Indian employed in the arsenal reported with severe gonorrhoeal arthritis in a knee, was admitted, and found to have endocarditis and chronic dysentery. His condition steadily deteriorated and death occurred about a fortnight later. Necropsy revealed three roundworms in the bowel and two entwined full length within the pancreatic duct. They probably were impacted. I was not sure of it, but Novis's case seems to raise the question whether the pancreatic duct may be a favourite haunt of *Ascaris lumbricoides*.

Posterior Pituitary and the Finger-nails

Dr. ALICE BUSH (Auckland) writes: A female patient aged 40 years presented with typical diabetes insipidus of one month's duration. The thirst and polyuria have been controlled for the past four months by injections of pitressin tannate in oil given at four- to five-week intervals. Early injections were followed by painful swelling of the breasts which was controlled by stilboestrol. This reaction does not now occur. The patient now informs me that since receiving the injections she has had to cut her finger-nails every week, whereas previously she found it necessary to trim them only once a year, as they did not grow. I have been unable to find any reference in the literature to the effect of the posterior pituitary on the growth of ectodermal appendages, and would be interested to hear whether others have had similar experience.

Vaccination Against Smallpox

Dr. C. K. MILLARD (Leicester) writes: I would like to make some brief comments on the statement of vaccination policy issued by the council of the Society of Medical Officers of Health (see *Journal*, September 15, p. 656). . . . Nothing is said about any alternative or supplementary measures such as hospital isolation and control of contacts, which have played such an important part during the past half-century. Would the writers of the statement have been so confident if these supplementary measures were not going to be carried out? . . . It so happens that in the February–March issue of the World Health Organization's *Epidemiological and Vital Statistics Report* there is a valuable monograph by Dr. M. Pascua, Director of the Division of Health Statistics, W.H.O., on "Evolution of Mortality in Europe during the Twentieth Century." In this he publishes a table showing the mortality from the principal epidemic diseases for each of the years 1901–49 in eight of the principal European countries. From this it appears that if we take the 44 years 1906–49 there is no country which had as low a mortality from smallpox as England and Wales. Yet during this period we have not depended upon vaccination of the population, which has been notoriously neglected, but upon hospital isolation and control of contacts. . . . The statement also says quite definitely that "on an outbreak of smallpox reliance should be placed on the selected vaccination of contacts and not on mass vaccination," but it goes on that "the medical officer of health should, however, bear in mind that, as soon as smallpox is first notified in his area, a demand for mass vaccination may arise from the public, and he should therefore plan at once the organization of such a measure." This may place a medical officer of health in a very difficult position. He is asked to prepare a measure in which he may not believe and which is not recommended by his society. Would it not be desirable that the Ministry of Health should issue much more definite instructions than it has done hitherto to strengthen an M.O.H.'s hands in refusing mass vaccination?

Obituary

J. B. HUNTER, C.B.E., *M.C.*, M.Chir., F.R.C.S.

Mr. J. B. Hunter, surgeon to King's College Hospital and the Royal Chest Hospital, died at his home at Epsom on September 16 after an illness lasting over a year. His passing will be mourned by a host of medical men, for he was a real friend not only of postgraduates but of innumerable students.

John Bowman Hunter was born on July 16, 1890. Educated at Bedford School, where he learnt the art of rugger, he went on to St. John's College, Cambridge, where he gained a first class in the natural sciences tripos. He continued his distinguished student career at University College Hospital, where he obtained the gold medal in clinical medicine. Qualifying in 1914, he served throughout the first world war and was an active campaigner, seeing service in France and Russia. He was mentioned several times in dispatches and awarded the Military Cross. During the war years Hunter made many friends both in the R.A.M.C. and in other units, for he was a friendly soul and was always ready to help in any emergency. Returning to University College Hospital after the war, he held a number of resident appointments and then became radium registrar: it was during this time that he became interested in radiotherapy in the treatment of malignant disease. In 1921 he graduated M.B., M.Ch., and also took the F.R.C.S. Hunter's inspiration was Wilfred Trotter, who was at the height of his fame at that time. They remained great friends, and it was Hunter who looked after Trotter in his last illness. It was always a surprise to Hunter's many friends in London that he was not appointed to the staff of University College Hospital, but he missed a vacancy by a very narrow margin. After leaving University College Hospital he was appointed to the Royal Northern Hospital and the Royal Chest Hospital, and it was at the latter that his early work on chest surgery took place. He later became thoracic surgeon to Papworth Sanatorium.

In 1928 Hunter was appointed to the staff of King's College Hospital. He was already well known to King's men, for he had married the daughter of Dr. Arthur Whitfield, who was dermatologist to that hospital. Hunter came to King's as an experienced surgeon, and he was a great addition to the staff, for he was a very sound practical surgeon who had been brought up in the Trotter tradition. His teaching rounds always attracted many students who were not on his own firm. He was joint editor with Sir Cecil Wakeley of Rose and Carless's *Manual of Surgery*, and he saw some five new editions through the press. The many articles he contributed to surgical journals were always full of interest and sound surgical common sense. He had no use for humbug, and was noted for his capacity for taking an infinite amount of trouble over his patients and their well-being.

Hunter was a good administrator, and his colleagues at King's recognized this by appointing him dean of the medical school within ten years of his joining the staff. In this office he built up a very sound medical school and enhanced its reputation. His own reputation was such that he became one of the representatives of the Faculty of Medicine on the Senate of London

University. At the Annual Meetings of the B.M.A. in 1931 and 1932 he was honorary secretary of the Section of Surgery. He later served on a number of the Association's committees, besides being a member of the Medical Planning Commission.

At the outbreak of the second world war Hunter was nominated group officer in charge of Sector VII of the Emergency Medical Service, and during the war years he not only dealt with the administration of the hospitals in his sector but did a vast amount of operating at King's and Horton. He also had to attend many committees of the University. At the end of the war Hunter was created C.B.E. for his services to the State.

It was during the war years that he was involved in a legal case in which an American patient brought an action against him and was awarded £6,300 damages by Mr. Justice Birkett. The whole medical profession was delighted when the Court of Appeal allowed Hunter's appeal, and in November last the House of Lords upheld the Court of Appeal (see *B.M.J.*, 1948, **2**, 537 ; 1949, **1**, 595, 669 ; 1951, **1**, 44). However, the years of worry over this case had a lot to do with the undermining of Hunter's health, and for the last year of his life he was subjected to constant attacks of cardiac asthma.

Hunter did many things in his life and held many important appointments, but he will always be remembered by his colleagues, students, and patients for his cheerfulness and his kindness. He will be missed in many fields, but especially at King's and at the University of London, where he was at one time deputy vice-chancellor. He is survived by his widow, who is a doctor, and by a son and a daughter.

C. G. LOWRY, M.D., F.R.C.S.I., F.R.C.O.G.

Dr. Hall Stewart writes : The death of Professor C. G. Lowry removes from our midst an outstanding member of the profession and of society, and it is fitting that an appreciation of him should be recorded at this time by a general practitioner—one of that large section of the medical profession which owes so much to him.

" C. G.," as he was affectionately called by his students and colleagues, was a man of great personality and one whose friendship was one of my most cherished possessions. Good surgeons can be trained, and Belfast has produced many of them, but a friend like Professor C. G. Lowry is a landmark in a lifetime. His presence brought with it a sense of security and courage when things were going wrong and a word of good cheer when the spirit flagged. Yet his students and house-surgeons would be the first to acknowledge that no one could administer a firmer rebuke than he when the circumstances demanded it. Many of us received those rebukes, and we are to-day better men and doctors because of them.

As a teacher he had few equals, and many of the aphorisms used by him in his university and clinical lectures crowd into my mind now as I think of him. He had the gift of imparting knowledge in a simple way, and was ever ready to help any student or young doctor who was willing to work. One standard of work only, however, was acceptable to him, and that was the best that could be produced.

I well remember, when I was his house-surgeon in the old Belfast Maternity Hospital, his righteous indignation at the standard of midwifery practised in our province then and the call he sounded so clearly for reform in this important branch of medicine. He then set himself the task of putting midwifery practice in Northern Ireland on a sound basis, and to-day the new Royal Maternity Hospital, and the teaching imparted to students and graduates there, stand as a memorial to him and to his achievements for the good of mankind.

As a student, house-surgeon, or general practitioner, one could not help being impressed by his efficiency, sincerity, and friendliness, for he had a genius for friendship that called forth from others feelings of affection and trust. His unfailing courtesy, his constant kindness, his gentle and human touch, and his thorough understanding of the patient's point of view, coupled with his outstanding ability as a surgeon, combined to make him the ideal consultant that he was acknowledged to be. Some men command admiration by their intellectual gifts ; others, perhaps fewer, attract by the magnetic charm of their personality. When these characteristics are combined in the same individual, as they were in C. G. Lowry, his influence is bound to be irresistible ; and so it was with him. His influence was, indeed, irresistible.

His name was, and still is, a household word in the North of Ireland. Honour after honour was thrust upon him, and yet, in spite of it all, he ever achieved without effort Sir William Osler's criteria for the well-balanced man—namely, " That equanimity which enabled him to bear success with humility, the affection of his friends without pride, and, when the day of grief and sorrow came, the courage to meet it like a man." As we general practitioners endeavour to carry on the torch lighted by him many years ago, we shall cherish many precious memories of him, and his influence will remain. We extend to Mrs. Lowry, his widow, and to his daughter, Mrs. C. H. G. Macafee, our sincere sympathy in our common loss.

The sudden death of Mr. ELLIS CAMPBELL BOWDEN on July 20 at West Moors, Dorset, came as a great shock to his friends and colleagues in Bournemouth and elsewhere. Born at Ramsgate in 1890, he was educated at St. Lawrence School, Ramsgate, and the London Hospital, where he qualified in 1913. After qualification he held several posts at the London, including those of house-surgeon, resident anaesthetist, senior clinical assistant, and surgeon to the out-patients department. During the first world war he served with distinction in the Middle East, and was awarded the Military Cross. After demobilization he held the appointment of resident surgical officer at the London Temperance Hospital, becoming a Fellow of the Royal College of Surgeons in 1921. Bowden then settled down in Bournemouth, where his father was also in practice, and was elected to the post of assistant surgeon at the Royal Victoria Hospital and West Hants Hospital in 1923, becoming full surgeon in 1937. He rapidly established a large consulting practice, and his ability as a careful and competent operator, combined with a very sound clinical judgment, gained for him a popular reputation among his fellow practitioners. He was vice-president of the Section of Orthopaedics at the Annual Meeting of the B.M.A. in 1934.

A colleague writes: Bowden's shy and reserved manner hid a great kindness of heart and thoughtfulness for his patients, who were quick to realize these qualities. He was transparently honest and straightforward, and worthily upheld the best traditions of the profession. His enthusiasms varied from sailing and flying to Egyptology. He retired early from the staff of the hospital to West Moors. It is a matter of great regret that he did not have longer to enjoy his country cottage and garden. Every sympathy will be extended to his widow.

Mr. THOMAS JOHN EVANS died at his home at Nottage, Porthcawl, on August 26, aged 39 years. He was born in the Rhondda Valley, and educated at Porth County School and the Welsh National School of Medicine. After obtaining the degree of B.Sc. he graduated M.B. (Wales and London) in 1937. During his university career he was extremely popular and took part in many student activities. In particular he was a good Rugby forward, playing for the medical school, the University of Wales, and for the Combined Welsh Universities touring team. He became house-surgeon, casualty officer, registrar to the radiotherapy department, and resident surgical officer at the Cardiff Royal Infirmary, and it was from this last post that he left the Infirmary to join the Royal Air Force Volunteer Reserve in 1941. A few months later he took the F.R.C.S. of Edinburgh and soon afterwards became a member of the team of orthopaedic surgeons working in the Royal Air Force. It was during this period that he made orthopaedic surgery his main interest and planned his future career accordingly. In October, 1945, he flew to Rangoon as surgeon to an R.A.F. hospital, but was invalided home in February, 1946. From that time he never left his bed. Although he knew the prognosis was poor, he bore his long illness with fortitude and serenity that were truly amazing. His morale throughout remained magnificent. He loved the mountains, the valleys, and the people of his youth. He was a good conversationalist and could activate the most lethargic mind so that a visit to Tom was always stimulating. By his death Wales has lost a surgeon of whom great things were expected. He will be missed sadly by many friends, and to his wife and two children we extend our deepest sympathy.—A. B. T.

Dr. TIMOTHY MICHAEL MCGRATH, manager of the *Cork Examiner*, died in Cork after a brief illness on August 31, aged 53. He studied medicine at University College, Cork, graduating M.B., B.Ch. in 1924. It was when he was in general practice in South Wales that the call came to join his father in the management of the *Cork Examiner*. After the death of his father in 1931 he became manager himself. A keen sportsman, he devoted some of his boundless energy to Rugby football. In Cork he became the "father" of the University College Club, whose president he was from 1934 to 1949, with one short break. In the wider field of administration he was no less active, being president of the Irish Rugby Football Union in 1947–8, the season when Ireland won the triple crown for the first time in 49 years. To his death he remained a member of the council and a trustee of the Union. Golf was his second love, and in turn he was committee member, captain, and honorary secretary of the Cork Club. Only a few weeks before his death he helped in large measure to make the Irish Amateur Close Championship at Cork an outstanding success.

Dr. W. J. Roche writes: Although he had long abandoned active practice, nowhere was the death of Dr. T. M. McGrath more keenly felt than in the medical profession. Into a comparatively brief span Ted McGrath had crowded a host of activities that made him a well-known figure in his native country and a welcome visitor in many parts of Britain. He combined in his person all the qualities that go to make men popular and respected. He was at once a medical colleague, a business man of high repute, and a lover of sport; and to all three he brought a kindliness of heart, a modesty of personal achievement, and an unselfishness of spirit that stamped him as a man above the ordinary. He laboured prodigiously for any cause that captured his interest, and he brought to bear on all his activities an unaffected charm of manner that made him a welcome figure in any gathering. Ted turned his back on what might have been a brilliant medical career for the sake of a long-standing and intimate family connexion with the *Cork Examiner*. He was an only son, and so, though it was with reluctance, he returned to Ireland to begin a new career when the call came. He mastered the intricacies of the newspaper business, and proved a worthy successor to a brilliant father. The care and management of a daily newspaper are not regulated by the clock, and Ted McGrath gave his services in full measure irrespective of the day or the time. Though it was inevitable that he should be thrust into the public eye because of his prominent association with Rugby football, it was characteristic of him that he preferred to work unostentatiously. Thus it was that few knew of his ardent work in the cause of charity. He had a particular interest in those afflicted with blindness, and devoted many hours each week to their welfare. Similarly, his services were freely placed at the disposal of the committee of a newsboys' club. Now that he has passed an abiding memory will remain of his unselfish devotion to worthy causes, of his infectious enthusiasm for the promotion of healthy minds in healthy bodies, and above all of the warm, kindly nature that endeared him to all fortunate enough to know him.

Medico-Legal

DECREE OF NULLITY AFTER A.I.H.

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

By English law, if at the time of marriage one of the parties to it is physically incapable by reason of an incurable condition of consummating the marriage, the marriage may be declared null and void by the court on the petition of the other party to it. Artificial insemination introduced unforeseen problems into this branch of jurisprudence by making it possible for a child of the parties to the marriage to be born without any consummation, with the result that if the marriage was subsequently declared null and void the child would be bastardized.

This point was argued in the first case of its kind to be dealt with by the courts.[1] In that case Mr. Justice Pearce held that, in spite of the birth of a child conceived by artificial insemination from the husband, and the consequence that a decree of nullity would bastardize it, there had been no consummation of the marriage by reason of a psychological impediment on the part of the husband which was, *vis-à-vis* his wife, incurable. He also held that the wife's main motive in resorting to artificial insemination was the hope that having a child might, as she had been advised by her doctor was possible, result in a cure of her husband's condition and the salving of their marriage. Accordingly she had not "approbated" the voidable marriage and was not debarred from relief by the principle that you cannot approbate and reprobate—that is, you cannot in law have your cake and eat it.

A similar case was decided recently in the Divorce Court by Mr. Commissioner Blanco-White.[2] The marriage took place in 1935, and the husband had proved to be impotent because of psychological trouble. The parties were advised that, if the wife had a child by means of artificial insemination, the husband's condition might be cured. A child was so born in 1945, but no cure was effected.

In declaring the marriage void the Commissioner said that he was satisfied that the wife had made it clear to her husband that she could not continue to live with him unless his condition was cured, and that she had consented to the artificial insemination only in the hope that it would be the means of effecting the cure. She had therefore not approbated the marriage.

The difficulty over bastardization of the child which had loomed so large in the arguments in 1949 has been solved by Parliament by s. 9 of the Matrimonial Causes Act, 1950. This provides that, where a decree of nullity is made in respect of a voidable marriage, any child that would have been legitimate if the marriage had been dissolved (that is, brought to an end at the date of the decree) instead of annulled (that is, declared never to have existed) shall be deemed to be the legitimate child of the parties.

[1] *British Medical Journal*, 1948, **2**, 1086.
[2] *The Times*, July 4.

INFECTIOUS DISEASES AND VITAL STATISTICS

We print below a summary of Infectious Diseases and Vital Statistics in the British Isles for the week ending September 8 (No. 36).

Figures of notified *cases* are for: (*a*) England and Wales (London included). (*b*) London (administrative county). (*c*) Scotland. (*d*) Northern Ireland. (*e*) Eire Figures of *births and deaths* and of *deaths* recorded under each disease are for: (*a*) The 126 great towns in England and Wales (London included). (*b*) London (administrative county). (*c*) The 16 principal towns in Scotland. (*d*) The 10 principal towns in Northern Ireland. (*e*) The 13 principal towns in Eire. A dash — denotes no cases; a blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, Northern Ireland, and Eire, the Ministry of Health and Local Government of Northern Ireland, and the Department of Health of Eire.

Disease	1951 Week Ending September 8					1950 Corresponding Week					1942–50 England & Wales Corresponding Week		
	(*a*)	(*b*)	(*c*)	(*d*)	(*e*)	(*a*)	(*b*)	(*c*)	(*d*)	(*e*)	Highest	Median	Lowest
Diphtheria	40	2	11	3	1	44	6	16	3	1	843	284	37
Deaths	—	—	—	—	—	—	—	—	—	—			
Dysentery	131	28	76	1		205	11	95	1		622	146	59
Deaths		—		—			—		—				
Encephalitis, acute	4	—	—	—		8	1	—	—		8	2	—
Deaths		—			—		—			—			
Erysipelas			15	3	5			21	4	4			
Food-poisoning	109	14		—		274	33		—				
Infective enteritis or diarrhoea under 2 years				14	45				12	18			
Deaths	10		—	2	1	18		4	1	1			
Measles*	1,387	50	71	69	36	2,530	162	96	32	71	2,646	1,321	535
Deaths		—	—	—	—		—	—	—	—			
Meningococcal infection	31	—	10	3	1	24	—	9	1	3	58	33	24
Deaths		—	1				—	—					
Ophthalmia neonatorum	27	2	11	—		32	3	9	—		95	63	32
Pneumonia, influenzal	196	15	3	5		192	10	2	3		318	268	192
Deaths (from influenza)†	5	3	2	—	—	6	1	—	—	—			
Pneumonia, primary			96					117					
Deaths	122	15		8	5	112	9		6	4			
Poliomyelitis, acute:													
Paralytic	47	2	11	4	1	513	35	76	14	2	708	28	13
Non-paralytic	39	3											
Deaths§	—	—			—	13	1			—			
Puerperal fever			5					8					
Puerperal pyrexia‖	231	27	3	—	1	54	5	15	1	2	160	117	54
Scarlet fever	499	28	157	16	15	658	58	127	45	46	2,436	833	540
Deaths		—	—	—	—		—	—	—	—			
Smallpox	—	—	—	—		—	—	—	—				
Deaths				—					—				
(1) Tuberculosis, respiratory			134	35				124	31				
(2) Tuberculosis, non-respiratory			19	4				29	6				
(1) Deaths	98	12	17	4	9	143	18	25	3	7			
(2) Deaths		2	3	2	1		4	6	1	2			
Typhoid fever	4	—	—	1	1	6	2	—	—	—			
Deaths¶	—	—	—	—		1	1	—	—		63	23	10
Paratyphoid fever	32	3	4 (B)	5		11	1	1 (B)	—				
Whooping-cough	2,576	124	344	56	88	3,682	280	311	31	98	3,682	1,683	1,077
Deaths	2	—	—	—	—	6	1	—	—	1			
Deaths (0–1 year)	195	26	27	5	23	204	23	33	6	14	345	305	205
Deaths (excluding stillbirths)	3,941	614	492	80	142	3,962	589	507	89	130	3,962	3,668	3,403
Annual death rate (per 1,000 persons living)			10·1					10·2					
Live births	6,753	1,179	824	233	423	6,836	1,104	780	203	409	8,784	6,837	5,811
Annual rate per 1,000 persons living			16·9					15·7					
Stillbirths	155	17	19			175	20	27			236	185	173
Rate per 1,000 total births (including stillborn)			23					33					

* Measles not notifiable in Scotland and returns are approximate. † Includes primary form for England and Wales, London, and N. Ireland. § The number of deaths from poliomyelitis and polio-encephalitis for England and Wales, and London (administrative county), are combined. ‖ Includes puerperal fever for England and Wales and for Eire. ¶ Deaths from paratyphoid fever are combined with those from typhoid fever.

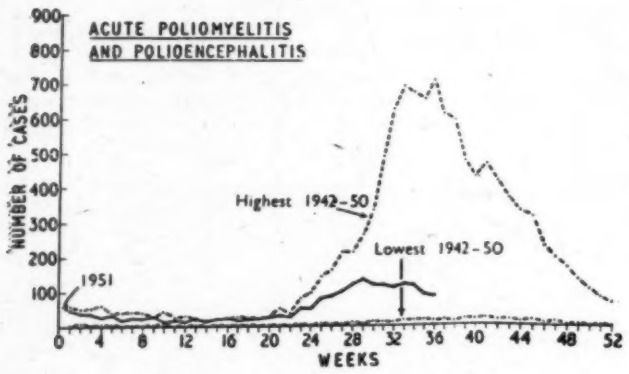
Vital Statistics

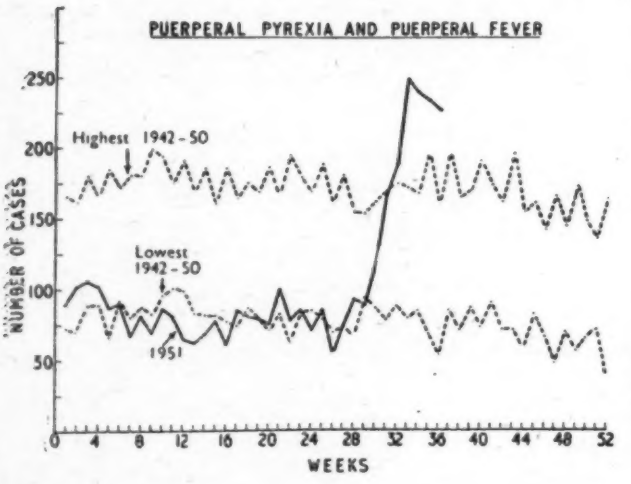
Poliomyelitis

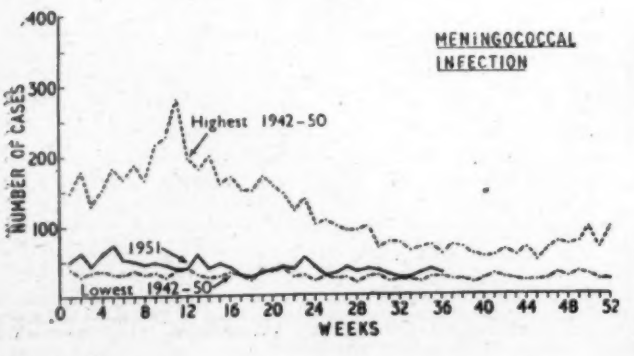
Poliomyelitis notifications in the week ending September 15 were as follows (figures for the previous week in parentheses): paralytic, 42 (47); non-paralytic, 48 (39); total, 90 (86). Non-paralytic cases formed 55.8% of the total notifications, which is a return to the general trend of the past weeks towards an abnormally high proportion of cases of this type of the disease.

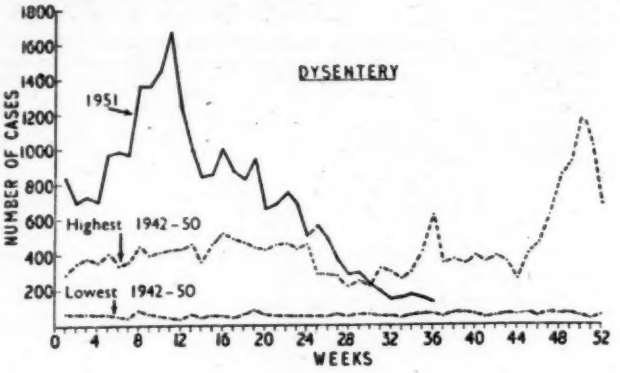
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported during the nine years 1942–50 are shown thus ------, the figures for 1951 thus ————. Except for the curves showing notifications in 1951, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Infectious Diseases

The chief variations in the trends of infectious diseases in England and Wales during the week ending September 8 were decreases in the number of notifications of measles by 489 and whooping-cough by 151, and a rise for scarlet fever of 38.

A decrease in the incidence of measles was reported from most areas of the country; the largest fall was 55 in Kent. The local trends of whooping-cough showed slight oscillations, but the only large variation was a decrease of 53 in the number of cases notified in Durham. The incidence of scarlet fever remained practically constant in most areas, the only change of any size being an increase of 30 in Lancashire.

The notifications of diphtheria were 5 more than in the preceding week; the chief features of the local returns were an increase of 5 in Lancashire and an increase of 4 in Staffordshire and in Worcestershire. The chief centres of infection during the week were Warwickshire (Birmingham C.B. 6) and Staffordshire (Coseley U.D. 5).

The notifications of paratyphoid fever were 5 fewer than in the preceding week. The only concentration of cases was 5 in Birmingham C.B.

Twelve more cases of paralytic acute poliomyelitis were notified than in the previous week, but the number of non-paralytic cases was 15 fewer. The largest returns were Lancashire 11 (Liverpool C.B. 3), Kent 7 (Gravesend M.B. 3), Yorkshire West Riding 7, London 5, Somerset 5, Gloucestershire 5, Warwickshire 5 (Birmingham C.B. 3), Northumberland 5.

The notifications of dysentery were 21 fewer than in the preceding week. The chief centres of infection were London 28 (Islington 17), Lancashire 20, Middlesex 16.

Low Infant Mortality

In 1950 the urban district of Harrow had the remarkably low infant mortality rate of 13.6 per 1,000 live births, of which there were 2,848. This is the lowest figure recorded for the district and is below even that for Hammersmith M.B. (17 per 1,000 live births) recorded in these columns on September 15 (p. 685). The comparable figure for London in the same year was 26.

Meningitis in County Durham

A few cases of meningitis are still being reported in County Durham. The outbreak began about the middle of July, and the disease runs a benign course. Similar cases have been seen in Cardiff and in Dorset. The causative organism has not been identified yet, and laboratory investigations are continuing.

Week Ending September 15

The notifications of infectious diseases in England and Wales during the week included: scarlet fever 595, whooping-cough 2,420, diphtheria 36, measles 1,211, acute pneumonia 212, acute poliomyelitis 90, dysentery 103, paratyphoid fever 38, and typhoid fever 10.

Universities and Colleges

UNIVERSITY OF EDINBURGH

Professor E. C. Kendall, Head of the Division of Biochemistry, Mayo Foundation, and Professor of Physiological Chemistry, University of Minnesota, who was awarded the Cameron Prize of 1951 jointly with Professor Tadeus Reichstein, will deliver a lecture in the Anatomy Lecture Theatre, University New Buildings, Teviot Place, Edinburgh, on Tuesday, October 9, at 5 p.m. His subject is "Hormones of the Adrenal Cortex in Clinical Medicine." Students and graduates are invited to attend the lecture.

UNIVERSITY OF LONDON

Professor Nicholson J. Eastman, Professor of Obstetrics and Director of the Department of Obstetrics, the Johns Hopkins University, will deliver two special university lectures in medicine. Lecture I on the "Premature Rupture of the Membranes: Its Bearing on Maternal Febrility and Infant Outcome" will be given at University College Hospital Medical School, University Street, Gower Street, W.C., on Friday, October 12, at 5 p.m. Lecture II on "Some Aspects of Caesarean Section" will be given at Guy's Hospital Medical School (Physiology Lecture Theatre), London Bridge, S.E., on Monday, October 15, at 5 p.m. The lectures are addressed to students of the University and to others interested in the subject. Admission is free, without ticket.

UNIVERSITY OF SHEFFIELD

Sir Francis R. Fraser, M.D., LL.D., F.R.C.P., Director, British Postgraduate Medical Federation, University of London, and Consulting Physician. St. Bartholomew's Hospital, will deliver the opening sessional address of the Faculty of Medicine in the Firth Hall of the University, on Thursday, October 11, at 5 p.m. His subject will be "Power and Responsibility."

ROYAL COLLEGE OF PHYSICIANS OF LONDON

A course of postgraduate lectures in medicine will be given at the College (Pall Mall East, London, S.W.) on various dates between November 14 and December 18, at 5 p.m. each day. The inclusive fee for the course is £4 4s. and the total entry is limited to 200. If accommodation permits, single lectures may be attended on payment of a fee of 10s. Fees are payable in advance and must be received at the College by November 1.

The Services

A *Supplement* to the *London Gazette* has announced the following awards:

First and Second Clasps to the Territorial Efficiency Decoration.—Major (Honorary Lieutenant-Colonel) W. A. Ball, T.D., R.A.M.C.

First Clasp to the Territorial Efficiency Decoration.—Lieutenant-Colonel F. J. Manning, T.D., R.A.M.C.

Territorial Efficiency Decoration and First Clasp.—Major R. J. S. Doherty, R.A.M.C.

Territorial Efficiency Decoration.—Major (Honorary Colonel) J. Bruce, Major (Honorary Lieutenant-Colonel) D. Jefferiss, and Captains (Honorary Majors) J. P. Heron and A. W. Raffan, R.A.M.C.

A statistical investigation of 15,000 poliomyelitis cases registered in Sweden in the period 1925–44 lends support to the theory that improved hygienic conditions increase the risk of the disease, according to a report by Professor G. Olin and Dr. N. O. Heinertz, of Stockholm, to the Congress on Infantile Paralysis recently held in Copenhagen. Children who live in crowded areas and are exposed to infection at an early age show increased resistance to the disease, the mortality being only 3.8% for infants up to 3 years, as compared with 23.7% for persons above 25 years of age. The statistics disclose that the majority of poliomyelitis cases in Sweden now occur at ages between 15 and 25, while the lowest rate is recorded for children under 5.

Medical News

The Heberden Oration

Dr. E. C. Kendall, professor of biochemistry in the University of Minnesota and one of the three recipients in 1950 of the Nobel Prize for Medicine, gave the Heberden Oration (which will be published later in this *Journal*) in the Old Library, B.M.A. House, on September 19. Sir Henry Cohen, the president of the Heberden Society, was in the chair. The Heberden Medal which he presented to Dr. Kendall is the first of a new design: it now bears on one side the figure of the great William Heberden, senior. Later on the same evening Sir Henry Cohen was the host at a dinner at which Dr. Kendall was the chief guest. The occasion was an informal one and the speeches were short. Sir Henry, proposing the health of Dr. Kendall, paid a sincere tribute to "the great biochemist from the continent beyond"; and Dr. Kendall, in a modest and humorous reply, alluded to some of the amusing results of the sudden blaze of publicity which he and his colleagues at the Mayo Clinic had to face after cortisone became headline news.

St. Dunstan's Physiotherapists

In his presidential address at the annual conference held at the beginning of September, Sir Neville Pearson revealed that there were now 125 practising war-blinded physiotherapists in Britain and there had been nine successful settlements in this country during the past year and three overseas.

Oliver Memorial Fund for Blood Transfusion

The fourth annual award of £50 from the Oliver Memorial Fund has been made to Mrs. Violet E. Smith, of Finsbury Park, London, who for many years has been associated with the organization of the Greater London Blood Transfusion Service and has herself a remarkable record as a donor. A special award of £25 has been made to Mr. Herbert Bruce, of Leyton, London, who has made repeated donations of blood for the preparation of testing serum, his being for several years the only known source in the world of Rh antibody anti-e. This service was rendered in spite of the fact that he was a sufferer from chronic anaemia.

Resettlement of the Disabled

The *Ministry of Labour and National Service Report, 1950*, contains an account of the work being done for the disabled. During the year two more industrial rehabilitation units were opened, and about 7,700 disabled persons were admitted for courses; the object of these courses is not to give direct vocational training but to restore the disabled to the highest degree of working fitness of which they are capable, and to test their suitability for various kinds of work. Under the Disabled Persons (Employment) Act employers with 20 or more people on their pay-roll are required to take 3% disabled persons. Employers in general are co-operative, as is shown by statistical returns, and although the Act does not apply to Government departments they were employing over 5.6% disabled persons during the year. The disablement resettlement officers attached to the Labour Exchanges continued to advise and help disabled men and women; about three-quarters of the job placings turn out to be permanently satisfactory. There was a continuous downward trend in the numbers of unemployed disabled persons during the year; in December, 1950, the number was the lowest recorded for some time—57,418, compared with 64,000 in the previous year. About 93% of all registered disabled people were employed in ordinary work, and approximately 1% in sheltered employment. Remploy factories continued to do valuable work, and the total of 92 factories will shortly be able to employ more than 8,000 severely disabled workers.

Streptomycin in America

Dr. Selman Waksman, of New Brunswick, has told the Paris Académie des Sciences that the United States is producing 11,000.000 g. of streptomycin a month (*Le Figaro*, September 12). The profits made on its manufacture are being used to create an institute for research in microbiology.

Emergency Bed Service: Applications and Admissions

During the seven days ending September 24 the number of applications made by doctors to the London Emergency Bed Service for admission of patients was 764, of which 90.18% were admitted.

Wills

Dr. Frederick Reginald Sutton left £13,767. He left his property upon trust for his wife for life, and then to the Royal Midland Counties Home for Incurables, Leamington Spa, and the Royal Medical Benevolent Fund.

Lieutenant-Colonel Wilfred Ernest Arbuthnot Armstrong left £83,614, and among other bequests £300 to the Victoria Hospital for Children, Tite Street, Chelsea, and the ultimate residue of his estate to the King Edward's Hospital Fund.

COMING EVENTS

Harveian Oration

Sir Archibald Gray will deliver the Harveian Oration before the Royal College of Physicians of London (Pall Mall East, S.W.) on St. Luke's Day (Thursday, October 18), at 3 p.m. His subject is "The Development of Dermatology from the Time of Harvey."

Edinburgh Lectures

A series of Honyman Gillespie Lectures has been arranged, in association with the Edinburgh postgraduate courses, to be given in the anatomy theatre, University New Buildings, Teviot Place, Edinburgh, on Thursdays at 5 p.m. from October 11 to December 6, both dates inclusive. The lectures are open to all graduates and senior students.

Public Health Lectures

A series of popular lectures on subjects relating to the public health will be delivered at the Royal Institute of Public Health and Hygiene, 28, Portland Place, London, W., on Wednesdays, October 17, 24, and 31, and November 7, 14, and 21, at 3.30 p.m. Admission is free, without ticket. Details will be published in the *Journal* week by week under "Societies and Lectures."

Simpson-Smith Lecture

The Institute of Child Health, University of London, has arranged for the Alex. Simpson-Smith Lecture for 1951 to be given by Professor E. D. Churchill, John Homans Professor of Surgery, Harvard University, and Chief of the General Surgical Services, Massachusetts General Hospital, at the Hospital for Sick Children, Great Ormond Street, London, W.C., on Friday, October 19, at 5 p.m. His subject is "Obliterative Bronchitis and Bronchiectasis." Admission is by ticket only, obtainable from the dean of the institute at the hospital.

John Shields Fairbairn Memorial Lecture

The John Shields Fairbairn Memorial Lecture will be delivered by Dr. Nicholson J. Eastman, of Johns Hopkins Hospital, Baltimore, U.S.A., before the Royal College of Obstetricians and Gynaecologists (58, Queen Anne Street, London, W.) on Thursday, October 11, 1951, at 5 p.m. His subject is "The Causes and Management of Premature Birth." Admission is by ticket only, obtainable from the secretary of the College.

Osler Club

The next meeting will be held on Friday, October 12, at 7.45 p.m., at the Medical Society of London, 11, Chandos Street, Cavendish Square. A symposium on man's experiments on man (in honour of Walter Reed, born September 13, 1851) will be opened by Dr. J. L. Burn with a tribute to Reed, illustrated by a film. Dr. G. W. M. Findlay will read a paper on yellow fever since Reed's discoveries, and Dr. Ancel Keys will read one on the Minnesota experiment on starvation.

Charing Cross Hospital Medical School

The inaugural address of the 1951–2 session of the Charing Cross Hospital Medical School will be delivered by Lord Inman at the Royal College of Physicians of London, Pall Mall East, S.W., on Friday, October 5, at 3 p.m. The prizes will be presented by Lady Inman.

Hospital Administration Refresher Course

A one-day course has been arranged for senior administrators by the Institute of Hospital Administrators on "The Ministry and the Hospitals" in the Great Hall, B.M.A. House, on October 20, at 10 a.m. Application should be made to Mr. M. Finlay, Tottenham Group Hospital Management Committee, The Green, N.15, before October 10.

Contraceptive Technique

A lecture and demonstration (on living models) on contraceptive technique will be given by Marie C. Stopes at the Mothers' Clinic, 108, Whitfield Street, London, W., on Thursday, October 4, at 2.30 p.m. Tickets must be obtained in advance, as space is limited.

Medical Art Society

The first meeting of the next session of the Society will be held at the Medical Society of London, 11, Chandos Street, W., on Friday, October 5, at 8 p.m., when Mr. Iain MacNab will attend. Medical practitioners interested in painting and drawing are invited to be present or to communicate with the honorary secretary, Dr. A. M. Rackow, 11, Hornton Street, London, W.8.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday

●ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—October 1, 5 p.m., "*The Diagnosis of Varicose Veins and Chronic Ulceration of the Leg*," by Mr. Harold Dodd; 6.15 p.m., "*The Surgery of the Sympathetic Nervous System in Peripheral Vascular Disease*," by Mr. Sol Cohen.

WESTMINSTER MEDICAL SCHOOL.—At Church House, Great Smith Street, London, S.W., October 1, 3 p.m., inaugural address of 1951–2 session by the Very Rev. John Lowe.

Tuesday

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—October 2, 5.30 p.m., "*Genetics*," by Dr. C. O. Carter.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—October 2, 5 p.m., "*The Painful Hip*," by Mr. Philip Wiles; 6.15 p.m., "*On Amputation of the Lower Limbs*," by Mr. Dudley Buxton.

Wednesday

GLASGOW UNIVERSITY: DEPARTMENT OF OPHTHALMOLOGY.—October 3, 8 p.m., "*The Eye in Hypertension* (1)," by Dr. R. Leishman.

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—October 3, 5.30 p.m., "*X-ray Technique*," by Dr. C. W. McKenny.

●INSTITUTE OF OPHTHALMOLOGY, Judd Street, London, W.C.—October 3, 4 p.m., inaugural lecture of new academic year by Sir Cecil Wakeley, P.R.C.S.; 7.30 for 8 p.m., at Rembrandt Rooms, 10, Thurloe Place, South Kensington, S.W., annual dinner (tickets 18s. 6d. each).

INSTITUTE OF UROLOGY.—At St. Paul's Hospital, Endell Street, London, W.C., October 3, 4.30 p.m., *"Infections of the Urinary Tract Other than Tubercle,"* by Mr. A. Clifford Morson.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—October 3, 5 p.m., *"The Surgical Pathology of Rectal Cancer,"* by Dr Cuthbert Dukes; 6.15 p.m., *"The Indications for and the Drawbacks and Dangers of Spinal Analgesia,"* by Professor R. R. Macintosh.

YORKSHIRE SOCIETY OF ANAESTHETISTS.—At the Leeds General Infirmary, October 3, 8 p.m., *"Breathing Space,"* by Dr. M. H. Armstrong Davison.

Thursday

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—October 4, 5.30 p.m., *"Histology of the Normal Skin,"* by Dr. H. Haber.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—October 4, 5 p.m., *"Carcinoma of Lung. A Clinico-pathological Study of 200 Resections,"* Hunterian Lecture by Professor J. Borrie; 6.15 p.m., *"Some Points in the Surgical Treatment of Goitre,"* by Mr. Vaughan Hudson.

Friday

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—October 5, 5.30 p.m., *"Eczema and Dermatitis,"* clinical demonstration by Dr. J. E. M. Wigley.

KING'S COLLEGE HOSPITAL MEDICAL SCHOOL, Denmark Hill, London, S.E.—October 5, 4.30 p.m., *"Legg and King's,"* Thomas Percy Legg Memorial Lecture by Sir Charlton Briscoe.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—October 5, 5 p.m., *"Crohn's Disease and Ulcerative Colitis,"* by Professor Charles Wells; 6.15 p.m., *"Trigeminal Pain,"* by Dr. S. P. Meadows.

ROYAL SANITARY INSTITUTE.—At Hastings Town Hall, October 5, 10.30 a.m., *"A Prospect of Public Health in a Cinque Port, with Particular Reference to Food Hygiene,"* by Mr. W. G. McDonald.

●WEST LONDON MEDICO-CHIRURGICAL SOCIETY.—At South Kensington Hotel, 41, Queen's Gate Terrace, London, S.W., October 5, 7.15 for 7.30 p.m., dinner meeting. Presentation of Triennial Gold Medal to Dr. C. H. Slocumb (Mayo Clinic).

WHIPPS CROSS HOSPITAL MEDICAL SOCIETY, Whipps Cross Hospital, London, E.—October 5, 8.30 p.m., *"What to Do with a Dead Body,"* by Dr. C. Keith Simpson.

APPOINTMENTS

NEIL, J. F., M.B., F.R.C.S.Ed., D.L.O., Consultant Ear, Nose, and Throat Surgeon to Nottingham General Hospital, Mansfield General Hospital, and Newark Hospital.

REYNARD, A. L., M.R.C.S., L.R.C.P., D.A., Consultant Anaesthetist at United Norwich Hospitals, East Anglian Regional Hospital Board.

STEWART, R. H. M., M.D., Deputy Senior Administrative Medical Officer, Newcastle-upon-Tyne Regional Hospital Board.

WHITTLES, J. H., M.D., D.P.H., Deputy Medical Officer of Health, City of Exeter.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Dossetor.—On September 3, 1951, at the South London Hospital, S.W., to Dr. Jill (formerly Acton Davis), wife of Dr. Andrew E. Dossetor, a son.

Smith.—On September 13, 1951, to Betty (formerly Gilbert), wife of Dr. B. J. Douglas Smith, of Quantock Lodge, Over Stowey, Somerset, a daughter—Rachel.

DEATHS

Allfrey.—On September 20, 1951, at Babbacombe, Torquay, Frederic Henry Allfrey, M.B., B.Ch.

Barlow.—On September 20, 1951, at 13, Egerton Road, Lincoln, Herbert Cecil Barlow, M.B., formerly of Minster Yard, Lincoln, aged 77.

Gilbertson.—On September 19, 1951, Albert James Gilbertson, M.B., B.S., of South Cliff, Roker, Sunderland, Co. Durham, aged 70.

Hodkinson.—On September 19, 1951, at a nursing-home, Samuel Hodkinson, M.B., Ch.B., of 36, Kent Road, Harrogate, Yorks, formerly of Ryhill, near Wakefield.

Isaac.—On September 15, 1951, Richard James Isaac, L.R.C.P.&S.Ed., L.R.F.P.S., of Derlwyn, Pontardulais, Glam, aged 77.

Jackson.—On September 13, 1951, at the Royal Lancaster Infirmary, Edward Siddall Jackson, M.B., Ch.B., of Robin Hill, Carnforth, Lancs, aged 59.

Kay.—On September 14, 1951, in hospital, Richard Kay, M.B., of 21, Manor Road, Bexhill-on-Sea, Sussex, aged 81.

Knobel.—On September 17, 1951, at his home, Spear Hill, Ashington, Pulborough, Sussex, William Bernard Knobel, M.D., M.R.C.P.

Manfield.—On September 20, 1951, at White Court, Alfriston, Sussex, Alwyne Harold Manfield, M.R.C.S., L.R.C.P., aged 69.

Windsor.—On September 12, 1951, at 2, St. Paul's Road, Cambridge, Frank Needham Windsor, M.B., B.Chir., Lieutenant-Colonel, I.M.S., retired, aged 83.

Any Questions ?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Multiple Papillomata of the Bladder

Q.—*I have a patient who has many recurrent seedling papillomata of the bladder, and he has been advised to have a transplantation of the ureters and cystectomy. He is a fit man in his early sixties. What is the risk of the operation and of the post-operative period? What is his probable future as regards continence by day and night? What sort of life will he be able to lead if all goes well?*

A.—Total cystectomy is the best surgical treatment for multiple papillomatosis too extensive for cystodiathermy. At this patient's age the tumours are probably already malignant even if of only a low grade of malignancy, but non-infiltrating growths will often respond to some of the newer methods of radiotherapy. The mortality of the operation of transplantation of the ureters and cystectomy is in the region of 10%, but this figure is diminishing under the influence of modern pre- and post-operative treatment and increasing surgical experience. The main post-operative risk in the early stages is of wound disruption and in the later stages of recurrent renal infection. This is usually controllable, and, provided there is no renal damage already, the function of the kidneys should remain satisfactory. Incontinence is very rare, although there is at first difficulty in distinguishing wind from water. Many patients can sleep through the night without disturbance, and most can lead a normal life. The risks must be weighed against the certainty of death from cancer of the bladder if the condition is left.

Roundworms in the Lungs

Q.—*What pulmonary symptoms, if any, does ascariasis cause in children or adults? Is there any abnormality in an x-ray picture of the chest?*

A.—In heavy infestations, especially in children, migration of ascaris larvae through the lungs about the second week after infestation may cause cough, even dyspnoea, blood-flecked sputum, or a frank bronchopneumonia, but ordinarily gross pulmonary symptoms and signs are uncommon with ascaris infection. Transient pulmonary infiltrations, with radiological changes and with eosinophilia, of the nature of Löffler's syndrome, have been suggested as sometimes due to ascaris infections.

Stinging by Jelly-fish

Q.—*What are the different jelly-fish likely to injure bathers round British coasts? Is anything known about the nature of their toxins?*

A.—The majority of jelly-fish in British seas are quite innocuous. This applies particularly to all the colourless ones (*Aurelia* and others), the stinging cells of which are much too small to penetrate the skin. Those slightly coloured brown (*Pelagia, Chrysaora*) can sting through the thin skin of a young child, but not through that of an adult. Their stings are in no way serious. The brown or dark-blue species of *Cyanea* are more powerful stingers and are about as bad as stinging-nettles, but they can be really uncomfortable only when they touch one's lips. It is very much a question of how thick the cuticle is which must be penetrated by the stinging cells. The only really dangerous form is the Portuguese man-of-war (*Physalia*), which occasionally drifts to the Cornish coast with the Gulf Stream. Extensive stinging by the tentacles of this may necessitate admission to hospital. Various toxic agents have been described from

jelly-fish and their allies. The stinging cells are said to contain tetramethyl ammonium hydroxide, which would be expected to have a curare-like action, but there is no clear proof that severe stinging is in fact due to this substance. Recent work by Emmelin and Feldberg (*J. Physiol.*, 1947, **106**, 440) has shown that the sting of the common stinging-nettle is due to concentrated acetylcholine together with histamine. The possibility that some similar complex amines may be in part the basis of the sting has not yet been thoroughly tested. There is some evidence that the stings of many of these animals are more complex than would be expected from a simple pharmacological substance. There are a number of phenomena which suggest highly specific immunity in some marine animals against the stinging-cell poison of particular species. Certain species of hermit crab and of fish seem often to show a specific immunity against the sting of a sea-anemone or jelly-fish with which they are associated; and indeed some crabs actually hold specimens of sea-anemones, to which they are immune, in their claws and use them to sting and collect other small marine creatures. Some very bad research work has been done on this aspect of the poisons. People have a way of grinding up a sea-anemone and injecting it into a rabbit: the rabbit dies, and they deduce the presence of "anemotoxin."

Climate and Rheumatoid Arthritis

Q.—*What is the present view of the effect of climate on rheumatoid arthritis? In which parts of England would a patient in an advanced chronic state of the disease be most comfortable and least likely to relapse?*

A.—Climate has no specific action in rheumatoid disease. The general health is more important in choosing a place to live, and so is personal choice from the psychological point of view. The popular idea that Algiers or Egypt is most suitable is mistaken. It is important to be within reach of relatives or friends rather than in a foreign country entailing a long and perhaps difficult journey. A hot climate is frequently trying, but changeable weather can also be trying; and equability so far as may be possible is desirable. Shelter from high winds, which seem to increase the pain considerably in many cases, should be sought. It is also important to choose a place where physiotherapy can be had and also social advantages in the way of entertainment. The inevitable depression of an invalid, crippled existence often matters more than climate, but country rather than town life will generally be more congenial. Damp is to be avoided so far as possible, but the sea coast is not contraindicated if the situation is not damp or unduly exposed. Rheumatoid patients are less susceptible than cases with fibrositis, and home comfort is more important than outdoor conditions in advanced chronic cases.

Ulcerative Colitis in the Tropics

Q.—*I have a patient who has suffered from ulcerative colitis for the past four years. At present she gets about two attacks of bleeding per year, needing rest in bed for about four weeks at a time. She is anxious to go to Singapore to live. Are conditions there suitable, from the point of view of availability of suitable diet, possibility of intestinal infections, etc.? Also, are there likely to be any public health restrictions in her case?*

A.—A patient suffering from chronic ulcerative colitis cannot be regarded as a good risk for life in the Tropics, where bowel disorders are particularly prevalent. Until properly acclimatized, even the healthy newly arrived European almost invariably suffers from some degree of enteritis or colitis. These are precipitated by the changes in climate, in diet, and in mode of life; by alterations in the intestinal flora; and often by infection with pathogenic bacteria or protozoa. A person suffering from a pre-existing colitis would almost certainly suffer from exacerbation of this as a result of, or in addition to, these intestinal upsets.

Conditions of life in Singapore in general are excellent for the physically fit; there would be no public health restrictions on the immigration of a case of ulcerative colitis.

A Gardening Problem

Q.—*A man has severe anaphylactic reactions to bee-stings. Is this a contraindication to immunization with tetanus toxoid or the administration of serum?*

A.—No. Sensitivity to bee-stings, in itself, is not a contraindication either to immunization with tetanus toxoid or to the administration of serum. There is no antigenic relationship between bee-venom and horse serum. Immunization with tetanus toxoid is to be recommended in allergic individuals to avoid the necessity of giving serum, to which a small proportion of allergic persons are highly sensitive.

NOTES AND COMMENTS

Tuberculous Endometritis and Pregnancy.—Dr. ALBERT SHARMAN (Glasgow) writes: In "Any Questions?" (September 1, p. 557) a question concerns the chances of a successful pregnancy in a case of tuberculous endometritis, and also the place of chemotherapy. Perhaps I may be allowed to contribute further information to the answers given, having on June 10 presented an invited communication (now in press), "Endometrial Tuberculosis in Sterility," concerning a study of 155 cases, to the American Society for the Study of Sterility. A follow-up of 122 patients who have been under observation for more than one year has shown that only one sterility patient with endometrial tuberculosis became pregnant. She became pregnant when 38 years old, after 17 years of marriage. The endometrial infection was detected in May, 1939; repeat biopsies in August, 1939, and in 1942 were both negative, although showing microscopic evidence of chronic endometritis. Another biopsy in 1948 showed no evidence of tuberculosis or even of chronic endometritis. The patient received no treatment, but pregnancy occurred in 1950. The patient went to full term and a normal healthy male child was born. Many of my cases have been followed up for five to eight years and one for 13 years. It is not surprising that in cases of endometrial-tubal tuberculosis the restoration of fertility is highly improbable, since (*a*) endometrial tuberculosis is virtually without exception secondary to tuberculosis of the tube, and (*b*) tubal occlusion was demonstrated to be present in 66.9% of 136 cases insufflated. Although this is the only known case of a successful pregnancy in a case of untreated tuberculous endometritis, it must modify critical appraisement if a case treated by chemotherapy should prove equally successful. The possibility of spontaneous "cure" in cases in which the tubes are not irremediably occluded must be borne in mind.

Intestinal Myiasis.—Dr. C. H. LADELL (Shirley, Surrey) writes: Travelling alone in the African bush, I passed a motion and noticed to my horror that it was swarming with maggots (see "Any Questions?" September 15, p. 688). By the evening I felt quite unwell, and moreover I had diarrhoea. However, a tobacco planter allayed my anxiety by informing me that locally it was a common experience, and that certain flies are viviparous, the larvae being deposited almost before defaecation is completed—a phenomenon which I subsequently verified.

Gone Abroad.—Professor F. J. Browne writes to say that he has left for Australia, where he will be living for at least three years at 211, Elizabeth Street, Sydney.

All communications with regard to editorial business should be addressed to THE EDITOR, BRITISH MEDICAL JOURNAL, B.M.A. HOUSE, TAVISTOCK SQUARE, LONDON, W.C.1. TELEPHONE: EUSTON 4499. TELEGRAMS: *Altiology, Westcent, London.* ORIGINAL ARTICLES AND LETTERS forwarded for publication are understood to be offered to the *British Medical Journal* alone unless the contrary be stated.
Authors desiring REPRINTS should communicate with the Publishing Manager, B.M.A. House, Tavistock Square, W.C.1, on receipt of proofs. Authors overseas should indicate on MSS. if reprints are required, as proofs are not sent abroad.
ADVERTISEMENTS should be addressed to the Advertisement Manager, B.M.A. House, Tavistock Square, London, W.C.1 (hours 9 a.m. to 5 p.m.). TELEPHONE: EUSTON 4499. TELEGRAMS: *Britmedads, Westcent, London.*
MEMBERS' SUBSCRIPTIONS should be sent to the SECRETARY of the Association. TELEPHONE: EUSTON 4499. TELEGRAMS: *Medisecro, Westcent, London.*
B.M.A. SCOTTISH OFFICE: 7, Drumsheugh Gardens, Edinburgh.